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RARE PERIPHERAL NERVE COMPLICATIONS IN OBSTETRICAL AND GYNAECOLOGICAL CONDITIONS

By

E. ADLER, M.D., A. JARUS, M.D. and A. MAGORA, M.D.[1]

The development of pain before and after delivery along the course of the sciatic nerve, without involvement of muscle power, is not an infrequent occurrence in an obstetrical department.

But there are few references in the literature with regard to peripheral nerve involvement of the lower limbs after delivery or gynaecological or surgical intervention (see comment). Most of these lesions are associated with anaesthesia, injections, toxic states, or conditions related directly to positioning during operation or labour.

During a relatively short period we have seen four cases with clear-cut motor lesions in the lower limbs, in which disturbances became manifest without any obvious cause other than delivery or gynaecological operation. We think it justified to give a more detailed account of these cases, because of their rarity and of the etiological problems involved.

REPORT OF CASES[2]

Case 1. N. Z., female, 32 years old, born in Yemen, came to Palestine in 1941.

Family history non-contributory.

In 1949 she was told that she had a duodenal ulcer, but she has had no complaints referable to this in the last three years.

Obstetrical history. There were seven pregnancies in all. Twelve years ago she suffered a spontaneous abortion, and then gave birth six times, one foetus being still-born. That was eight years ago and the baby weighed 1500 gr. All the other children weighed 2500 gr. at birth except the last, who weighed 3000 gr.

On the 9th Dec. 1952 the patient was admitted to the Obst. Dept., of the Hadassah Hospital, Jerusalem[2]. She complained of slight pain and swelling in her right leg. Because labour did not advance sufficiently for a multipara, the patient's

---

[1] Department for Physical Medicine and Rehabilitation, Hadassah University Hospital and the Hebrew University Hadassah Medical School, Jerusalem.

Dr. E. Adler is Associate Professor and Dr. A. Jarus and Dr. A. Magora junior members of his staff.

[2] We are indebted to Dr. Bromberg of the Dept. of Gynaecology and Obstetrics for referring the four cases to us.

TABLE 1

Muscle	12/18 52	12/25 52			1/5 53			4/6 53			2/17 54
	M.P.	M.P.	El. Ex.		M.P.	El. Ex.		M.P.	El. Ex.		Chron.
			d.	id.		d.	id.		d.	id.	
r. inner hamstrings	f	n	F	F	n	F	F	n	F	F	
r. outer hamstrings	f	g	F	F	g	F	F	g	F	F	
r. gastrocnemius	p	g	F	F	n	F	F	n	F	F	
r. posterior tibial ...	O	p	F	F	f	F	F	n	F	F	
r. toe flexors	p	g	F	F	n	F	F	n	F	F	
r. anterior tibial	O	O	D.	D.	O	D.	D.	O	D.	D.	19,4 ms.
l. anterior tibial	n	n	F	F	n	F	F	n	F	F	0,78 ms.
r. peroneals	O	O	D.	D.	f	F	F	n	F	F	
r. toe extensors	O	g	F	F	n	F	F	n	F	F	

M.P. Grade of muscle power (O zero, p poor, f fair, g good, n normal).
El. Ex. Electrical Examination (d. direct, id. indirect).
Chron. Chronaxie.
F faradic.
D. Degeneration Reaction.

pelvis was x-rayed and this revealed a relative disproportion between the pelvis and the foetal head (the conjugata vera was 9 cms., that is 1 cm. narrower than the accepted normal).

Despite this, intervention was decided against and after seventeen hours labour the patient delivered a slightly asphyxiated child weighing 3000 gr.

Immediately after delivery, she complained of severe pain, tingling, and weakness in the muscles of her right leg. Thrombophlebitis developed in this leg, and this was treated for eight days with Dicumarol with excellent results.

Examination (18.12.52). There were no pathological findings on general examination.

Neurological examination showed severe hypaesthesia and hypalgesia in the area innervated by the right common peroneal nerve, a reduced right ankle jerk, and weakness of the hamstrings, the dorsal and plantar flexors and extensors of the toes (Table 1).

She was immediately put on a course of daily active and passive excercises, and was given electrical stimulation by means of interrupted galvanic currents.

It should be stressed here that at no time during or after labour did she receive any anaesthetic or injection or undergo instrumental manipulation. Her legs were not tied.

Seven days later muscle power was examined again and electrical testing was carried out (Table 1).

On January 1953 she was examined once more and general improvement was found (Table 1). Muscle power was increased generally except for the tibialis anterior muscle, the ankle reflexes were equal on both sides, and there was less sensory disturbance in the same area.

The patient was discharged but continued ambulatory treatment in our Outpatient Dept.

Three months later (6th April 1953) the patient was examined again (Table 1)

TABLE 2

Muscle	Case II		Case III		Case IV	
	$^{7}/_{3}$ 53	$^{4}/_{6}$ 53	$^{8}/^{8}$ 53	$^{28}/_{11}$ 54	$^{15}/_{9}$ 53	$^{10}/_{4}$ 54
	M.P.	M.P.	M.P.	M.P.	M.P.	M.P.
r. Iliopsoas	g	n	n	n	n	n
l. Iliopsoas	f	n	f	n	f	n
r. Sartorius	g	n	n	n	n	n
l. Sartorius	f	n	f	n	f	n
r. Quadriceps	t	n	n	n	n	n
l. Quadriceps	f	n	g	n	f	n

Key as in Table 1. In addition: t traces.
Electrical Examination see text.

and no abnormalities were found except for slight hypaesthesia over the outer lower third of the calf, severe weakness of the tibialis anterior, and slight weakness of the biceps femoris.

The patient discontinued treatment and was next seen again (for a different complaint) in February 1955, when examination revealed essentially the same state as was found before. The electromyography done in the m. tibialis anterior showed fibrillation and a few fasciculations at intended work, and a few fibrillations at rest and in the m. biceps femoris rather low voltage (Fig. 1). The chronaximetry was distinctly prolonged in the m. tibialis anterior (Table 1).

Case 2. R. C., a female, 21 years old, born in Israel, married, no children, clerk by profession.

There are no relevant facts in her past or family history.

Diagnosed as suffering from an acute abdomen, she was operated upon and paraovarian cysts were found. A bilateral paraovarian cystectomy, and appendectomy, were performed. The operation which was done under general anaesthesia, was uneventful and one day later on trying to get out of bed, she found that she could not stand up owing to weakness of her legs. She also complained of a peculiar sensation in both thighs.

On examination, muscular weakness of both thighs and hypaesthesia over the anterior and medial portions thereof were found (Table 2).

Both patellar reflexes were absent. Otherwise there were no other abnormal findings. Laboratory examinations were normal.

Electrical testing one month after operation showed normal responses of the femoral nerve and its branches to galvanic and faradic currents. Electromyography was normal.

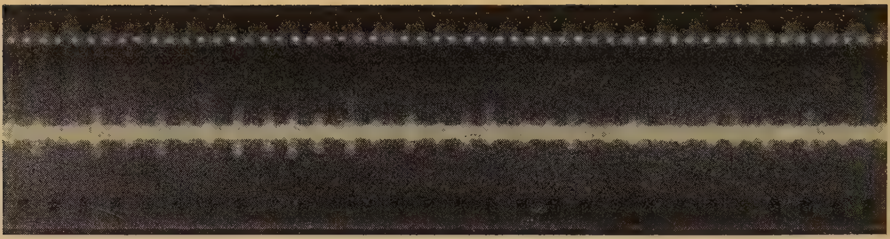
The prognosis was considered to be good in this case. She was given galvanic stimulation and exercises of the affected muscles.

Three months after operation she regained her muscle power and the patellar reflexes also returned but remained weak.

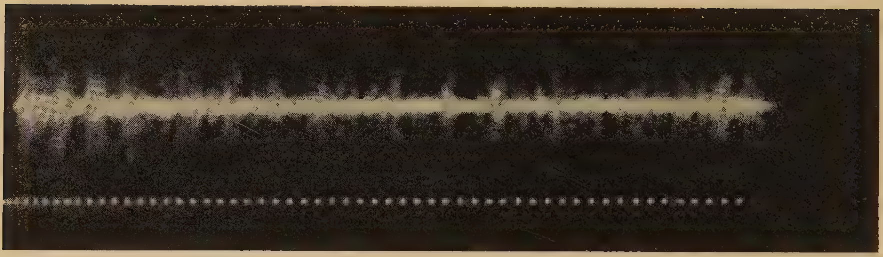
Case 3. S. A., a female, 24 years old, born in Iraq, married, no children.

The past and family history did not disclose any relevant features.

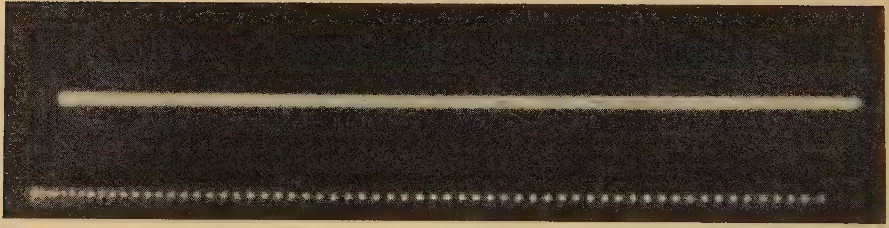
The patient was operated upon for the removal of a left paraovarian cyst.



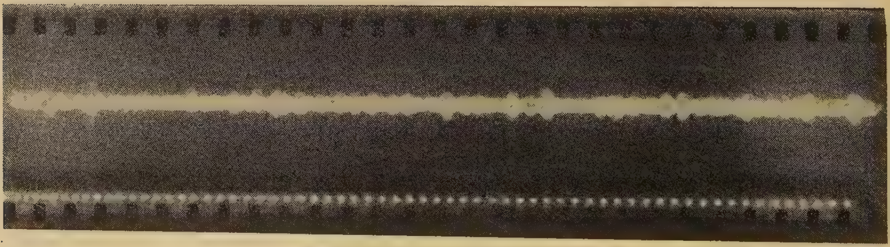
R. anterior tibial muscle at rest.



R. anterior tibial muscle at intended work.



R. biceps femoris at rest.



R. biceps femoris at work.

Fig. 1.

Cystectomy, wedge section of the left ovary, and appendectomy were performed under general anaesthesia.

One day after operation she complained of numbness of her left lower leg and, on trying to get out of bed, found that she could not stand on her left leg as it bent under her.

On examination, hypaesthesia in the distribution of the left femoral nerve, weakness of the thigh muscles (Table 2), and absence of the left patellar reflex were found.

Electrical testing twenty days after operation showed normal responses from the femoral nerve and its muscles to galvanic and faradic stimulation. Electromyography of the left quadriceps muscle was normal. This patient was given the same treatment as those described above and examination three months and a half after operation revealed no pathological findings.

Case 4. V. B., a female, 28 years old, born in Poland, married, one child, nurse by profession.

Four years previously she had had an extra-uterine pregnancy on the right, which was operated upon without any complications ensuing.

She was operated upon under general anaesthesia for the removal of a left extra-uterine pregnancy. One day after operation, on trying to get out of bed, her left leg bent under her, and she complained of loss of sensation on the inner side of her left foot.

On examination, weakness of the muscles of her left thigh (Table 2), absence of the left patellar reflex, and hypaesthesia of the inner side of her left foot were found.

Electrical examination performed a fortnight after operation showed absence of response to faradic current from the femoral nerve to the quadriceps muscle and a normal response to galvanic current with the rheobase slightly elevated. The patient refused electromyography.

She was given the same treatment as the other patients in this group, and six months after operation she was perfectly well.

COMMENT

It appears that the first patient developed a rather rare form of sciatic nerve palsy (in the form of neuroapraxy and partial neurotmesis) as a consequence of delivery, though cases of sciatic pain or even slight weakness are fairly common.

Many cases have been described of sciatic nerve palsies following oil or intraneural injections, or compression, such as tying the thighs during operation or delivery, but no recent report of severe sciatic nerve palsy during delivery has been found, although almost all text books of neurology refer to such a possibility.

According to *A. B. King* (1), possible causes of sciatic or lumbosacral nerve palsies include pressure of the foetal head, prolonged labour, narrow pelvis, and an overweight foetus. He mentions that pain is possible before, but that the palsy appears during or after the delivery. He states that recovery is generally incomplete and that one or more of the dorsal flexors remain weak. He describes only twenty cases seen by him, ten of whom developed disabilities during delivery, and of these only a few were sciatic cases. In the present patient the palsy appeared immediately after delivery, though there was some pain before she was admitted to hospital. The delivery was rather prolonged for a multipara, lasting seventeen hours. There was some discrepancy between the foetal head and the pelvis, and the child weighed 3000 gr., i.e. about 500 gr. more than the previous children. As a proof that the sciatic nerve lesion occurred in the pelvis, where the nerve leaves the lumbo-sacral plexus, it may be mentioned that its four branches—the two branches to the hamstrings, common peroneus, and the tibialis—were injured, whereas had the lesion been lower, the two branches to the hamstrings would not have been affected, as they leave the sciatic nerve immediately after its emergence from the plexus.

It is worth while stressing that the frequently encountered sciatica-like pain which develops before and after delivery does not constitute the main feature in this case, being only incidental to a severe prolonged motor disturbance.

On the other hand, the femoral lesions in the three other cases, are of the neuroapraxic type, apparently of gynaecological origin.

This infrequent form of nerve injury raises an intriguing problem, as on the whole the femoral nerve is one of those least liable to injury by any of the usual causes.

Wilson (2) quotes a figure of 1.78 % for femoral injuries sustained in war, while *Adler* and *Beller* (3) found 3.9 % of similar injuries among 126 cases of peripheral nerve war injuries seen by them.

Apart from war injuries *Kroll* (4) describes the following as causative factors for femoral nerve injury; luxations, fractures, tumours, neuritis, postoperative scars or adhesions, inflammation of the female genitalia, and traction of the nerve during gynaecological operations in the small pelvis, particularly under anaesthesia.

De Jong (5), *Wilson* (2), *Grinker* and *Bucy* (6) list the same conditions as causes of femoral nerve lesions. *A. B. King* (1) dealing only with complications in pregnancy, mentions that damage to the femoral nerve may occur during delivery through pressure of the thigh on Poupart's ligament, at the point where the nerve leaves the pelvis.

It seems worth mentioning that *J. B. Lyons* (7) reported eleven cases of peripheral nerve involvement due to haemophilia, seven of whom showed signs of femoral nerve palsy. In his opinion the cause was a haematoma in the ilio-psoas muscle.

Although the femoral nerve in its course is protected by the psoas muscle and is anatomically rather distant from the field of gynaecological operations, it nevertheless seems evident to us that the operation itself, perhaps aided by anaesthesia and its consequences, was the cause of these three palsies. Additional evidence for this is shown by the fact that in all three cases the ilio-psoas muscle was clearly involved, indicating that the pressure on the femoral nerve was above Poupart's ligament, as the branch to the ilio-psoas muscle leaves the nerve high up in the pelvis. Furthermore, it is beyond the bounds of coincidence that after a bilateral operation the palsy was bilateral, and after two unilateral operations the palsy was also unilateral, and on the side of the operations.

It seems obvious that either distant pressure (instrumental) or an intramuscular haematoma is to be blamed for the lesions described above which were in all cases transitory.

Thirteen years ago one of us (E.A.) encountered an analogous case of femoral nerve injury after histerectomy for a myomatous uterus. This patient recovered after six months with appropriate treatment.

SUMMARY

Peripheral nerve palsies in the lower limbs are reported in connection with obstetrical and gynaecological procedures. The sciatic nerve palsy was proved to have occurred during delivery, and the femoral nerve palsies developed following gynaecological operations.

The relevant literature and the pathogenesis, kind of treatment, and prognosis are referred to.

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CULTIVATION OF NERVOUS TISSUE IN THE CEREBROSPINAL FLUID OF PATIENTS SUFFERING FROM MEGALOBLASTIC ANEMIA WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

By

P. Ermala, M. Siurala, L. Siimes
and P. Reissell

Although thus far it has not been possible definitely to explain the pathogenesis of the hematological changes occurring in pernicious anemia, experimental studies in this field have advanced so far that the clinical and therapeutic management of anemia is possible. Paradoxically, however, there has been an increase in the relative incidence of combined neurological changes. It has not been possible directly to adapt the results of hematological therapy, nor has it even been conclusively demonstrated to what extent, if at all, the neurotropic and hematopoietic factors are identical. Likewise we do not know the pathogenesis of subacute combined degeneration of the spinal cord with markedly similar pathological changes but with a non-anemic etiology found in a great variety of conditions of disease. Thus, for instance, in the reviews by *Bremer* (1936) and by *Woltman* and *Heck* (1937) 64 different diagnoses are given.

Already from the point of view of method, the study of the neurological changes involve considerable difficulty. This is one of the reasons for the small number of investigations carried out. The reactions of the hematopoietic organs are very rapid and their observation is therefore readily possible by, e.g., the peripheral blood picture, examination of the bone marrow, etc., whereas neurological investigations have had to be based only on changes in the clinical condition, which develop

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very slowly and are difficult to interpret. Thus it is hard to determine the extent to which negative therapeutic results may be a result of the irreversibility of the lesions. The cultivation of nervous tissue *in vitro*, however, appears to offer a suitable experimental method. Nevertheless, this method has not been employed earlier, and the present work therefore is of an orientative nature in this respect.

Spinal cord tissue of human embryos was cultivated *in vitro* in the cerebrospinal fluid of normal persons as well as of patients suffering from megaloblastic anemia with combined subacute degeneration of the spinal cord, special attention being paid to quantitative differences in the growth of the tissue.

MATERIAL AND METHODS

The tissue material was derived from a total of 4 normal human embryos obtained by *sectio minor* performed for therapeutic abortion in the Women's Clinic, University of Helsinki. The length of the embryos (mento-calcaneal diameter) was as follows: A – 16 cm, B – 18 cm, C – 12 cm, D – 21 cm, the term of gestation having thus been about 3½ to 4½ months. Explant was made as soon as possible after the gynecological operation, at the latest within 2 hours. During this time the embryos were stored in the original amniotic fluid in the refrigerator at + 4° C. The lumbar part of the spinal cord was dissected out and as carefully as possible divested of the meninges and of any blood possibly extravasated on its surface in order to prevent the development of fibroblastic tissue. The original site of the nervous tissue in the spinal cord could not be defined exactly, but efforts were made to take the specimen from the dorsal column. The tissue material was cut out into pieces measuring roughly 1 mm along each side, which were explanted into Carrel dishes on solid medium prepared according to a modified method by *Burt*. With the end of a hot test tube a paraffin ring 1 cm in diameter was stamped on mica. Inside this ring a thin film was made by adding a drop of saline solution containing agar-agar. The piece of tissue was placed in the center of the hardened film and covered with cerebrospinal fluid, 0.2 cc in each dish. The solid medium was compounded as follows: NaCl 5.80, KCl 0.15, $CaCl_2$ 0.15, Mg · $6H_2O$ 0.075, NaH_2PO_4 0.038, dextrose 4.00, Phenol red trace, agar-agar *q.s. ad gelatinos.*, distilled water *ad* 1000.0. Immediately before use the pH was adjusted to 7.4 by the addition of a 1 per cent solution of $NaHCO_3$ until the phenol red indicator was of the proper colour. The cultures were incubated at + 37° C for 8 days, the liquid medium being changed daily. 20 to 30 samples were taken from each embryo for the

TABLE 1

	Group I				Group II	
Patient No.	1[1]	2	3	4	5[1]	6
Age	41	49	46	48	64	69
Hematological changes:						
Hb (corrected Sahli)	64	81	50	54	68	65
RBC × 10^6	2.44	2.64	1.61	2.03	2.37	2.20
Colour index	1.33	1.56	1.52	1.35	1.42	1.48
WBC × 10^3	2800	3950	3150	1350	6000	3550
Megaloblasts	+	+	+	+	+	+
Free HCl	—		—	—		—
Neurological changes:						
Disturbances of superficial sensibility: upper limbs	+	+	+	—		
– – – lower limbs	+	+	+	—		
Disturbances of deep sensibility: upper limbs	+	—	+	+		
– – lower limbs	+	+	+	+		
Disturbances of reflexes	+	+	—	—		
Brain and cranial nerve symptoms	—	—	—	—		
Autonomic and trophic manifestations	+	+	—	—		
Incoordination	+	—	—	—		

[1] Tapeworm anemia.

parallel cultivation of 10 samples each in normal cerebrospinal fluid and pathological fluid. A total of 100 cultures were studied in this manner (Table 2).

The tissue cultures were examined daily and quantitative measurements of the growth were made from unstained specimens as shown in Fig. 1. The distance from the margin of the explanted, solid tissue piece to the outermost zone of growth was measured and then in five different places at even intervals (at angles of about 60°) and the average of these dimensions expressed in millimeters, was taken as the final reading.

In the method of cultivation employed, histological staining of nervous tissue is not possible. For this reason a few experimental cultures were made by the hanging drop method according to *Maximow*. Quantitative observations cannot be made from these cultures, however, but staining of the preparations is possible. This was done after fixation in Bouin's fluid, using the protargol-gold chloride method of *Bodian*.

The cerebrospinal fluid was obtained from 6 patients suffering from untreated megaloblastic anemia which in 2 cases was tapeworm anemia.

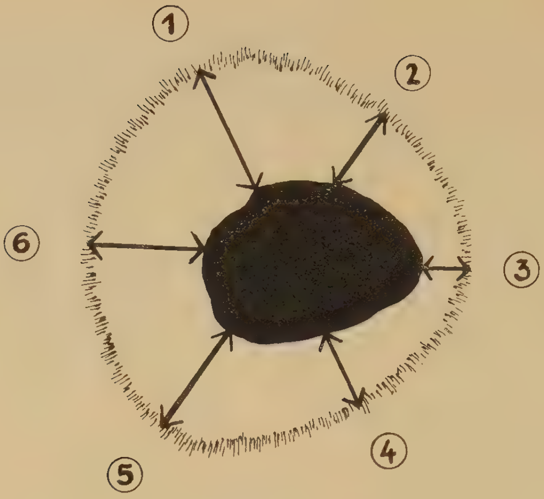

Fig. 1.
Method for determination of the growth.

Severe neurological changes were present in 4 cases (Table 1). Cerebrospinal fluid from 4 normal persons of the same age (40–50) was used as controls. All the test persons were males, and the patients were all hospitalized. The cerebrospinal fluid samples were drawn by lumbar puncture before the commencement of the specific treatment.

RESULTS

Definite differences were seen in the growth of the tissue in the normal and pathological media. The results obtained after maximum incubation for 7 days are shown in Table 2 and the mean daily quantitative progress in growth in each group will be seen from the graph in Fig. 3.

The differences between groups I and III as well as between groups I and II are significant ($P<0.01$)[1]. When cerebrospinal fluid of patients suffering from megaloblastic anemia with combined spinal cord degeneration was used as culture medium, tissue growth was considerably poorer than in cerebrospinal fluid from normal patients of the same age group. On the other hand, growth in the fluid of anemia patients without neurological changes was nearer to the limits of the normal material, showing only a possible certain difference ($P<0.1$). In view of the small series available no conclusions can be drawn in connection with the severity of the neurological changes or regarding the etiology and duration of the disease. Growth was almost equal and relatively

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[1] *Student*'s t-test has been applied for statistical treatment of the results.

TABLE 2

Series of patients	Tissue growth in milimeters				
	Embryo A	Embryo B	Embryo C	Embryo D	Mean
Group I: Anemia with neurological changes					
Patient No. 1 ...	0.61				
„ „ 2 ...		0.34			
„ „ 3 ...			0.86		
„ „ 4 ...				0.62	0.60 ± 0.093
Group II: Anemia without neurological changes					
Patient No. 5 ...	0.90				
„ „ 6 ...		1.62			1.26 ± 0.122
Group III: Normal controls					
Patient No. 7 ...	1.23				
„ „ 8 ...		2.10			
„ „ 9 ...			1.86		
„ „ 10 ...				1.49	1.67 ± 0.109

rapid in all the groups during the first three days but then stopped in group I.

The growth of nervous tissue, in general, was typical, as described earlier by several authors (cf. *Bauer*). Already a few hours after explantation numerous fine filamentous threads can be observed, which grow into the medium. There are some variations in the lapse of time between explanation and the first evidence of growth from culture to culture, but this always occurred at the latest within 5 to 10 hours. No differences were obtained between the main groups. If a long time has elapsed since the surgical operation—in this case the sectio minor—commencement of growth is delayed. The nature and origin of the first threads cannot be seen because of the thickness of the tissue explant and because growth may start at any depth. Morphologically, also, the brush of filamentous processes produced by glial cells is very similar to the growth of neurites and it is at first difficult to distinguish it. The neural fibers originate partly from the regeneration of cut nerve fibers and partly from the differentiation of neuroblasts. The neurites are of a relatively even thickness and their free ends are enlarged by active amoeboid movement and extend very slender pseudopods. As growth proceeds filaments of all elements form plexa, which may be quite dense.

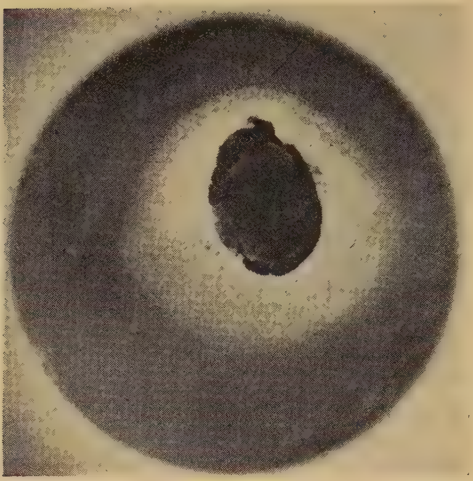

Fig.2.
Tissue culture after incubation for a week.
The explanted piece of tissue has been removed.

Very soon there occurs migration of various cells, mainly neuroglia, neuroblasts, or more differentiated nervous cells, microglia, fibroblasts and macrophages, and around the tissue piece a membraneous zone of new growth with distinct margins is formed.

At the initial growth phase, which also quantitatively was equal in all groups, no morphological differences were seen. After three days' culture, however, changes soon began to appear between the normal and the pathological groups. In the cultures containing normal medium the tissue growth proceeded with no morphological changes. There continued to be migration from the margin and straight radial fibrillary growth. In the pathological medium, on the other hand, growth was retarded, especially of the oligodendroglia and protoplasmic astroglia cells. The growth of fibres was very sinuous and irregular plexa were formed. The size of the cell itself was smaller than usually, which points to the probability that pseudopodic growth took place at the cost of the cell protoplasm without actual increase in the substance of the cell. The method used will not permit determination of the rate of mitosis. However, tissue growth and the mitotic rate are not parallel phenomena.

Contrary to most other types of tissue, which readily become dedifferentiated *in vitro,* the nerve cell usually continues differentiating. For this reason their lifetime is relatively short and there soon occur degenerative changes. Such changes became evident also in the normal cultures on the 8th or 9th day of incubation. There were indications,

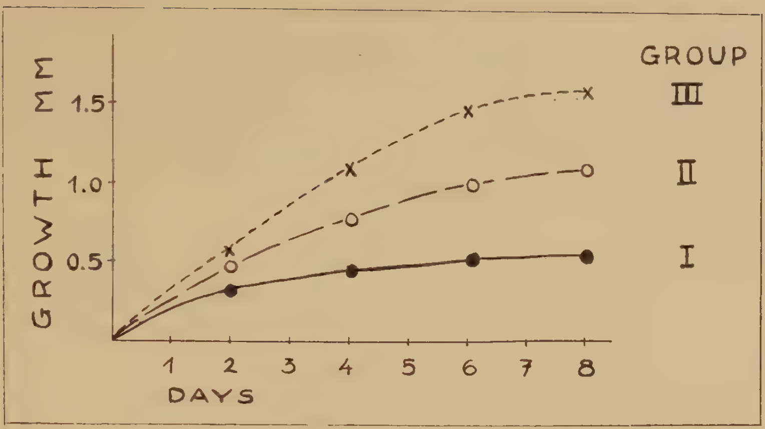

Fig. 3.
The daily rate of growth. Group I: pernicious anemia with neurological changes, Group II: pernicious anemia without neurological changes and Group III: normal controls.

furthermore, that several of the migrating cells in the pathological medium, especially those resembling oligodendroglia, had perished already in the earlier days of cultivation. Degeneration begins in the cell body with the appearance of clear vacuoles. The fibrils remain distinctly normal even to the last stages of degeneration.

DISCUSSION

As always in tissue cultures, we are not here concerned with "growth" in the ordinary sense of the word, i.e., increase and enlargement of living protoplasma, but this is a more complicated phenomenon. The migration and spreading out of the tissue cells in the medium represent the greatest contribution to the "growth" and chiefly consist in the active functioning of the tissue. The formation of fibres, also, is not in normal cases merely a pseudopodic spreading of the cell protoplasm, since adequate decrease in the size of the cell was not discerned in normal cases, as far as perceivable with the method used. The rate of mitosis could not be determined, but this is not of great significance when tissue of the central nervous system is concerned.

Thus the differences in growth are referable to changes in the vitality of the tissue, i.e. in some of the normal active functions of the cells. When pathological cerebrospinal fluid was used as culture medium, disturbances particularly occurred in the development of macroglial cells. It is of course true that tissue grown *in vitro* cannot directly be compared with normal tissue. There are, however, some interesting similarities when observations are compared with the histopathological picture occurring in combined acute spinal degeneration. Characteristic of fresh lesions is demyelination with total destruction of the myelin sheath in small limited patches, and destruction of the axis cylinder occurs only later. The disease is mainly localized in the posterior and lateral fasciculus.

In seeking an explanation of inhibition of nervous tissue growth in our cultures two main probabilities may be considered: a toxic inhibitory factor in the pathological cerebrospinal fluid or a deficiency of necessary growth factors.

Evidence of the presence of toxic factors in pernicious anemia as propounded by a large number of investigators is still uncertain. *Lajtha* (1950), in using different dilutions of pernicious anemia serum for bone marrow cultures, found the ripening of megaloblasts inhibited and ascribed this to the presence of an inhibitory factor. *Feinman et al.* (1952), however, were unable to corroborate this finding in corresponding experiments. There is even less knowledge of the existence of an inhibitory factor acting on the nervous system. The exacerbation of neurological changes during pteroyl-glutaminic acid (PGA) treatment have been attributed by *Ross et al.* (1948) to the inhibitory action of PGA on the glutaminic acid metabolism of the nervous system. On the other hand, *Cobb et al.* (1942) found that recrystallized PGA has no effect on the oxygen consumption by at least rat brain tissue, although it should be remarked that the method employed by them apparently was inadequate. Extensive experimental studies concerning the toxic factors in the pathogenesis of pernicious tapeworm anemia have been made by *Tötterman* (*e.g.*, 1944), who was able to produce hematological changes by peroral or parenteral administration of lipid extracts of Bothriocephalus, especially of the lycolecithin fraction.

The deficiency theory has been generally accepted as the most probable one, supported particularly by the successful results obtained in hematological therapy. Comprehensive clinical and experimental works on tapeworm anemia have been published by *Bonsdorff* and his associates (cf. *Björkenheim*, 1951). A fuller review of the literature is not possible here, and reference is made, e.g., to the extensive survey by *Welch* and *Heinle* (1952) of the metabolic effects of the hematopoietic factors. A review of the neurological factors is given by *Björkenheim* (1951).

The observations from tissue cultures described in this report offer no definite indications in either direction, but the circumstance that growth was at first nearly similar in the normal and the pathological groups speaks rather for the theory of deficiency than for that of a toxic agent.

The cerebrospinal fluid evidently plays an important, but for the present little known, role in the metabolism of the central nervous system. *Martinovic* (1931) used normal homologous cerebrospinal fluid as the medium in cultivating cat brain tissue. He made no quantitative comparisons with cultures in other tissue fluids or culture media, but the morphological picture given by him does not show noteworthy differences from, for instance, the plasma experiments described by other workers. Spinal cord tissue of human embryos has been cultivated in the cerebrospinal fluid of normal human adults by *Ermala*. The cerebrospinal fluid was found to possess a growth-promoting factor which is not present in plasma and which is a non-nutritive, but chiefly bio-catalytic, "growth-hormone". Tissue growth was greater in normal serum than in pure cerebrospinal fluid. However, when a medium containing equal proportions of the serum and the cerebrospinal fluid of the same person, growth definitely exceeded that obtained in similar amounts of pure serum. The cisternal fluid proved to some extent more effective than that drawn by lumbar puncture. *Ungley* (1949) in his therapeutic experiments found that brain tissue contains a substance ameliorating the neurological manifestations in pernicious anemia but lacking anti-anemic effect. *Agostini* (1952) was able to observe some reticulocytogenetic factors in the cerebrospinal fluid of subjects in whom he had stimulated the diencephalic hemoregulation centres by electro-shocks.

The possibility that neurological disturbances are caused by the lack of one or more purely neurotropic factors not identical with hematopoietically active substances, has been put forward by several authors (*Salus* and *Reiman,* 1934; *Björkenheim,* 1951). So far, however, no definite proofs have been presented. It appears probable that since vitamin B12 has a therapeutic effect on neurological changes (*West et al.,* 1949; *Schieve et al.,* 1949; *Ungley,* 1949) it would also constitute the primary factor, the deficiency of which would produce hematological and neurological changes. Although the metabolic effect of B12 and other hematopoietically active factors has been the subject of extensive research, their definite mechanism of action is not known with certainty. In therapy it has been possible to substitute B12 and PGA by nucleinic acids, which are assumed to be the final products of the whole complicated metabolic process (*Nieweg et al.,* 1952; *Vilter et al.,* 1951), and by the basic constituents of these acids, such as thymine, thymidine, etc.

As stated above, vitamin B12 exerts a therapeutic action on neurological changes as well, or at least it arrests the process. PGA, on the other hand, does not produce this effect, but it rather aggravates the neurological condition (*Heinle et al.*, 1947; *Wagley*, 1948), although its simultaneously hematopoietic action is uncontested. It has therefore been suggested (*Nieweg et al.*, 1952) that PGA and B12 influence the synthesis of different nucleinic acids—the former that of desoxyribose nucleinic acid and the latter that of both ribose- and desoxyribose nucleinic acid. *Hyden et al.* (1948) have demonstrated the importance of ribose nucleinic acid for the metabolism of the normal central nervous system, and by clinical observations *Haenel* (1950) has indicated that disturbance in the metabolism of ribose nucleinic acid would be the direct cause of neurological disorders. PGA and desoxyribose nucleinic acid, on their part, would be indispensable for the maintenance of normal erythropoiesis. According to *Ross et al.* (1948) the normal cerebrospinal fluid contains only a minimal amount of B12 or none at all. Determinations on pathological fluid have not been published. It is also generally conceded that the cerebrospinal fluid in anemic spinal cord degeneration remains clinically normal (protein, cells).

The present knowledge thus suggests the probability that inhibition of the growth of nervous tissue in pathological cerebrospinal fluid *in vitro* is a result of a deficiency of vitamin B12 or of ribose nucleic acid and its preliminary constituents. The tissue culture seems to offer a serviceable method for closer analysis of the various factors by means of substituting experiments.

SUMMARY

Spinal cord tissue of human embryos was cultivated *in vitro* in the cerebrospinal fluid of normal persons as well as of patients suffering from megaloblastic anemia with combined degeneration of the spinal cord, special attention being paid to quantitative differences in the growth of the tissue.

When pathological fluid was used as culture medium, tissue growth was considerably poorer than in cerebrospinal fluid from normal patients. The difference is statistically significant.

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PRIMARY PERIVASCULAR CEREBRAL, CEREBELLAR AND LEPTOMENINGEAL MELANOMA

(Congenital Aphasia and Familial Predisposition to Nævi Verrucosi)

By

SIMON FISCHER

INTRODUCTION

Melanoma was first described in 1864 by *Virchow* (26) as a spindle cell sarcoma, often of a more carcinomatous stamp.

Secondary metastatic melanomas of the central nervous system are so comparatively common that every large institute of pathology has one case a year.

On the other hand the primary melanomas of the central nervous system are rare. In 1941 *E. Christensen* thus mentioned that, so far, 6 cases had been reported (5). In 1947 *Strong* (26) stated that till then 37 cases were found in the literature of the whole world. This considerable rise in the number of cases reported was not only due to the passage of time, or to a greater interest being taken in the primary melanomas; it was also due to the establishment of other, less strict criteria according to which the primary and secondary melanomas of the central nervous system were distinguished.

There is apparently a difference between the pathogenesis of the primary and that of the secondary intracranial melanomas; only the pigment is a common characteristic. The primary tumours thus apparently do not metastasize in spite of their close relation to the vessels. They are less well-defined, have a tendency towards diffuse, especially meningeal, growth, and are therefore more inclined to recur *in loco* owing to subtotal extirpation. Furthermore, the histological picture of the primary melanomas is not so polymorphous as that of the secondary ones may be. The origin of the primary melanomas is considered mesodermal, arising from melanophores, whereas the secondary tumours are generally supposed to be neuro-ectodermal.

The original criteria of distinction between the primary and secondary melanomas were strict (*Lubarsch* (17) 1920), as cases of intracranial melanomas in patients with a simultaneous conspicuous cutaneous nævus should be considered secondary in the central nervous system. *Farnell, Globus* and *Willis* (12) were more moderate; they mentioned cases with primary leptomeningeal melanosis in addition to a resting nævus pigmentosus, which is frequently known in the skin. *Willis* (27) also mentioned that ramified pigment cells are found under normal conditions in the meninges, especially on the base of the brain, and in particular in coloured people. *Obersteiner* and *Rokitansky* (23) demonstrated the presence of pigment cells along the pial vessels, enveloping them like peritheliomas, possibly originating from the perithelial cell demonstrated by *Eberth* (8).

Several authors consider the following theories of the origin of the pigment cells to be possible:

(1) The perivascular theory, according to which the pigment cells arise from the adventitia of the vessels or from the endothelium of lymphatic vessels (*Herzog* (13));
(2) The chromatophore theory, according to which the pigment cells are of mesoblastic origin (*Ribbert, Virchow* (26));
(3) The neuro-epithelial theory, according to which they originate from the senso-cutaneous nervous apparatus (*Masson, Oberndorfer* (20));
(4) The perineural theory, according to which the pigment cells are derived from cells along sensitive nerves (*Foot, Bjørneboe* (4)).

In 1880 *Demieville* (7) was the first to mention the possibility that nævus cells might originate from vascular epithelium. The intimate relation to the vessels has been established histologically, and is peculiar. During more recent years, blood-tinged or xanthochromic spinal fluid has actually, in accordance with this observation, been ascertained especially often in primary, though also in secondary, melanomas of the central nervous system, and it has been attempted to take practical advantage of this. If traces of blood are found in the spinal fluid, it is recommended, in the case of reasonable suspicion of the presence of a tumour, to look for melaniferous tumour cells. With regard to the frequency of blood in the spinal fluid, it is said that there is no difference between primary and secondary melanomas; but the presence of blood is about 10 times more frequent in melanomas than in the case of ordinary metastases to the central nervous system (*Madonick* and *Savitsky* (18)).

CASE REPORT

A boy, B. P., born in July 25th, 1947, died on December 31st, 1953, in Department B, Frederiksberg Hospital. Autopsy No. 2/54: No familial predisposition to cancer, epilepsy, or intellectual inferiority.

The patient's maternal grandfather had had several verrucose nævi of the skin, but died of asthma. The patient's mother also had two similar nævi, one on the left shoulder, measuring about 1 × 1 cm, and one, measuring 5 × 5 cm and about 2 cm in height, almost in the midline of the lumbar region. These nævi had been growing throughout her life without giving rise to symptoms. The patient's father had been suffering from a disease resembling haemophilia but without familial occurrence; at the age of 29 he died of internal haemorrhages caused in an accident. Two siblings, aged 8 and 10 years, had no conspicuous nævi, and were in completely good health. The members of the family were medium blonde with a slight reddish tinge of the hair.

The patient was the third of three children. He was born at term, rapidly and normally after a completely normal pregnancy. Immediately after delivery, several flat nævi were noticed, namely on the sole of the right foot, in the right gluteal region, where it measured about 3 × 3 cm, and in the right scapular region. He had been otherwise completely well-shaped, and physically he later developed normally, though he was of somewhat slight build. His mother supplied the following information: His appetite was not good. He was incredibly restless, had been playing best on his tricycle or with his broom. He sometimes withdrew in solitude, holding his hands on his head. He was unable to speak, could at best say father and mother, but recognized and remembered things he had seen before. Walking, running, and food habits were normal for his age. He might be vehement occasionally, but never malicious. In the opinion of strangers he was always a queer child. His mother had never noticed signs of impairment of vision.

At the age of two months he suddenly had from four to six daily fits of convulsions of one minute's duration; these were both tonic and clonic convulsions of muscles of the face and the extremities, accompanied by cyanosis and foaming at the mouth. He was subfebrile with slight redness of the pharynx, and had somewhat liquid motions. After about five weeks the general practitioner therefore sent the patient to Medical Department B, Frederiksberg Hospital, on October 29th, 1947, for gastro-enteritis, pharyngitis, convulsions (rachitic tetany?). He was in hospital for a fortnight. He ran a high temperature for three days, and the diagnosis of febrile convulsions was therefore also considered here. He soon improved in hospital, but after his discharge still had absences of one or two minutes' duration up to five times monthly at the utmost.

He had occasional colds with redness of the tonsils, a slight rise of temperature and cough. On June 23rd, 1948, he was admitted for one day for examination in the Ear, Nose and Throat Department of Frederiksberg Hospital; the angular lymph nodes were found to be enlarged and firm. 16 months later, on November 7th, 1949, he was again in the same department for five days to have tonsils and adenoid growths removed. Histological examination of tonsils and adenoid tissue: Hypertrophy of the tonsils, adenoid growths. (2667/49). Revision of preparations: no melanophores.

At the age of 5 ½ years, in February, 1953, he was admitted permanently to the State Institute for Speech-Defectives, as he was still unable to say a word except "mother". He extended his vocabulary, but was unable to form a simple sentence. He was assessed as mute but hearing, as audiometry was normal. His intelligence was estimated as normal by a psychologist.

In September, 1953, he developed attacks of chiefly left-sided pain in the head, occasional semiconsciousness, crying, and wandering and squinting of the left eye. There was increasing anorexia and loss of weight. On December 17th, 1953, the patient was unable to stand up, he vomited, showed grinding of his teeth, and had cold shivers. The doctor ascertained rigidity of the back and the neck, and the patient was therefore admitted on the same day to the Isolation Department of Blegdamshospitalet. He stayed there for 5 days under the diagnosis: observation for mumps meningitis. Kernig's signs was positive. His face grimacing. The lower extremities were held in a position of strong flexion with good strength; the patellar reflexes were brisk, there were no definite pareses. Examination of the eyes and ophthalmoscopy: no coarse disturbances, the fields of vision could not be determined. The cerebrospinal fluid contained blood (accidental admixture?), and showed 365/3 monocytes, numerous red blood corpuscles; glucose 102 mg per 100 ml. The temperature fell, and the patient was discharged before Christmas.

During the days that followed he had attacks of crying and sleeplessness and was shaking his head. On the morning of December 31st, 1953, he was unconscious, cyanotic, with shallow breathing and a rise of temperature to 39° C. After 6 hours he was therefore admitted to Medical Department B, Frederiksberg Hospital. There was no rigidity of the neck or of the back. The optic axes were parallel. The pupils were dilated and did not react. The extremities were flaccid with absence of reflexes. The spinal fluid showed xanthochromia: 19/3 cells, albumin 100, globulin 30, glucose 112 mg per 100 ml; cultures were sterile. Auscultation of the lungs: pneumonic changes at the base of the left pulmonary region. The patient died 5 hours after admission.

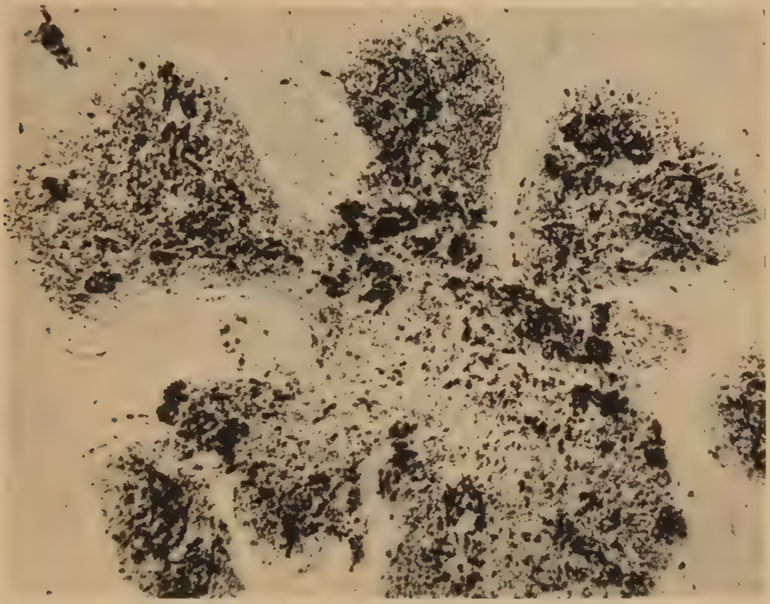

Fig. 1.
Cerebellum, intense subcortical pigmentation with tumour tissue in latent growth phase. 40: 1.

AUTOPSY DESCRIPTION

An asthenic, medium-blonde boy. Two blackish brown spotty nævi were seen below the left ear, two or three hairy nævi were present on the left upper arm, and on the left thigh.

Slightly purulent bronchitis and bronchopneumonia in the left lower lobe were the most essential findings in the organs.

The pathological findings in the brain may be mentioned systematically:—

The *skull* was normal.

Vessels: the basal arteries were thin-walled, without aneurysms.

Meninges: the leptomeninges appeared universally changed; they were whitish, slightly thickened, especially at the reflections of the pia mater in the sulci, though sufficiently translucent for the vessels to be seen. The membranes were separated manually with some difficulty where they adhered to each other, for instance along the first portion of the anterior cerebral arteries in the intercerebral fissure and along the middle cerebral arteries in the lateral cerebral fissure. The membranes were thickened in the following parts: the left inferior and superior gyri frontales, over the right central sulcus, corresponding to the cisterna pontis et interpeduncularis and the cisterna magna. Fresh subpial haemorrhages were seen in the following areas: the gyrus orbitalis dxt. and the pars orbitalis gyri frontalis sup. dxt.

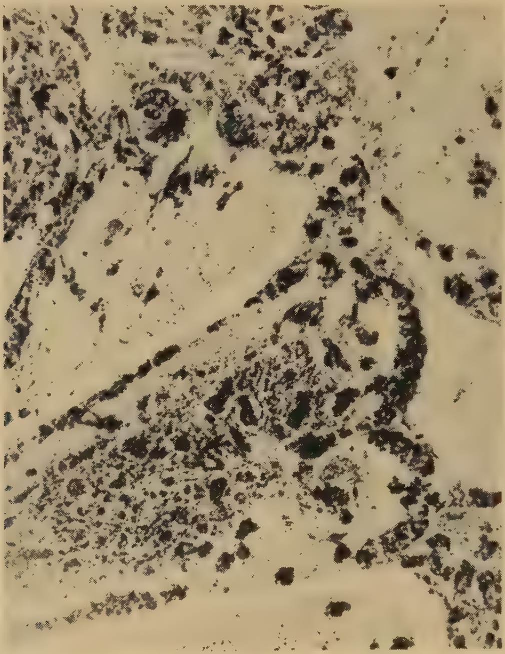

Fig. 2.
Cerebellum, tumour tissue in active growth phase with diffuse meningeal growth and perivascular cortical localization. 40: 1.

Luschka's and Magendie's foramina were normal.

The *brain* measured 18 ½ × 17 × 15 cm. Sections showed multiple, focal, emolliated areas, localized to the grey substance, especially the cortex, parasagittally on the convexity, and on the base of the brain. These changes appeared in greyish white, brownish, and reddish brown shades or were frankly haemorrhagic.

The following cortical changes were seen:—

On the right side, corresponding to the pars orbitalis gyri frontalis sup. dxt., a haemorrhagic focus (1), measuring 3 × 4 mm, and corresponding to the lobulus paracentralis dxt. upwards in the intercerebral fissure, a greyish brown process (2), measuring 6 × 7 mm, and, in the gyrus occipito-temporalis med. et lat. dxt., punctate brown foci (3). On the left side, corresponding to the pars superior gyri frontalis medius sin. a brownish area (4), measuring 2 × 3 mm; further, corresponding to the pars opercularis gyri frontalis inf. sin., a greyish brown area (5), measuring 3 × 4 mm, and at the left superior gyrus frontalis, posteriorly involving the precentral gyrus, a brown area, measuring 5 × 5½ cm; this was fairly well-defined, localized in the cortex, but from this area an almost vertical slit-like bloody emollition, measuring 6 cm in depth, extended towards the base, partly undermining the postcentral gyrus. In the adjoining gyri, corresponding to the middle frontal gyrus, slight, superficial emollitions (6) were seen; corresponding to the pars superior insulae sin., a greyish brown area (7), measuring 4 × 4 mm; at the gyrus circumflexus sin., a punctate brown focus (8); and at the gyrus occipito-temporalis med. sin., a brown focus (9), measuring 4 × 5 mm.

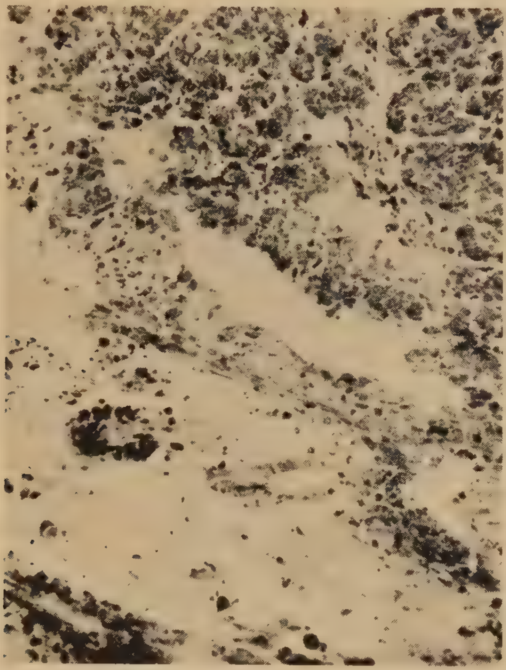

Fig. 3.
Cerebellum, tumour tissue in active growth phase with perivascular subcortical localization; melanotic and amelanotic forms. 75: 1.

The following deeper cerebral changes were seen:—

On the right side, corresponding to the right thalamus, two brown foci, measuring 1 × 2 mm, localized in the lateral and medial nuclei, respectively, and a three-sided brown process of a maximum width of 5 mm in the vault of the posterior horn of the right lateral ventricle in relation to the optic tract and the cauda nuclei caudati (10).

On the left side, almost symmetrical with the preceding process, another process the shape of an inverted V was seen in the vault of the posterior horn of the left lateral ventricle in relation to the optic tract and the cauda nuclei caudati (11); finally, corresponding to the left thalamus there was a three- sided, brown area of a maximum width of 5 mm, extending wedge-shaped over the medial towards the lateral nucleus across the bundle of Vicq d'Azyr (12).

The cerebellum.—The right hemisphere measured 2 × 5 × 5 cm, and was rather flattened. In the cortex of the inferior semilunar lobule there was a greyish white, round, tumour-like mass, measuring 4 × 5 mm. The outlines of the nucleus dentatus were reddish brown. The left hemisphere measured 1 × 4 × 4 cm, and was much flattened, except for a humpy, protruding tumour, measuring 14 × 20 mm, in the inferior semilunar lobule; it was chiefly localized in the cortex. Sections of the tumour showed that it was greyish white, round and well-defined. The outlines of the nucleus dentatus were brown. In the anterior portion of the quadrangular lobe there was a brownish, irregular area anteriorly, measuring 3 × 3 mm. Haemorrhages were seen in the cortex cerebelli of the uvula and the pyramis vermis.

The brain stem.—A brownish, translucent area, localized in the right vestibular area, was seen in the rhomboid fossa. Sections showed fresh haemorrhages between the transverse fibres and the pyramidal tracts on either side in the anterior half of the pons.

Supposed cerebral pathophysiology (the figures correspond to those mentioned in the autopsy description):—

Psychic disturbances (1); right homonymous hemianopsia, left-sided increase of tonus, left-sided spontaneous coordination movements, left-sided anaesthesia or loss of deep sensibility (10); cortical blindness (3); opposed disturbances of coordination of the ocular muscles, namely affection of the levator palpebrae and rectus lateralis muscles (1) and (4); disturbances corresponding to Broca's centre with opposed partial pareses of the pharynx and the musculature of the tongue (5); left-sided hemianopsia, right-sided increase of tonus (11); right-sided anaesthesia and loss of deep sensibility, left-sided disturbance of olfactory tracts (12); disturbance of association between heard and spoken words (7); right-sided tonic and clonic convulsions of the extremities and right-sided conjugate turning of head, eyes, and body, possibly paresis of the right leg (and of the right arm, and right-sided anaesthesia owing to disconnection of the corticopetal tracts) (6); disturbance of the optic centre of perception with optic aura, opposed tonic convulsions in conjugate eye movements (9); disturbance of association between sounds and visual impressions (8).

Supposed cerebellar pathophysiology:—

(Bilateral or hemilateral symptoms, as the left hemisphere was macroscopically most affected). Homolateral decrease of tonus, nystagmus and dysmetria with scanning speech and zigzag gait.

Supposed pontine pathophysiology: Affection of the right vestibular nucleus (Deiter's nucleus), and possibly of cochlear tracts with disturbances of hearing and of vestibular function. In addition, affection of pyramidal tracts causing bilateral pareses, spastic increase of tonus with tonic reflexes of the neck, clonus, and a positive Babinski's sign. Finally, affection of the pontine centre of conjugate eye movements, partly of the abducens nucleus and partly of the association tracts, the medial longitudinal fasciculi, causing the patient to squint.

The clinical symptoms were:—

A. Fits of suffocation and convulsions at the age of two months (probably caused by the meningeal tumour tissue, hardly post-partum anoxia, fever, or rachitic tetany).

B. Disturbances of speech when the patient was about two to three years old (pars superior insulae Reilii sin. with affection of association tracts between Wernicke's and Broca's centres).

C. Headaches, chiefly in the left side, and semiconsciousness (minute haemorrhages in the left cerebral hemisphere) during the last three months of the patient's life.

D. Squinting of the left eye (affection of the pontine centre of conjugate eye movements) during the last three months of life.

E. Grinding of the teeth (affection of the motor nucleus princeps nervi trigemini in the upper part of the pons) during the last three months of life.

F. Rigidity of the neck and of the back (meningeal localization of the tumour tissue in the fossa cranii posterior and the vertebral canal (?)) during the last ten days of life.

G. Hyperreflexia and flexion of lower extremities (affection of pyramidal tracts and incipient spinal automatism) during the last ten days of life.

H. Dilated pupils (interruption of association paths between the pontine centre of conjugate eye movements and the small oculomotor nucleus) during the last 24 hours of life.

I. Flaccid pareses (tetraplegia?), impairment of breathing (fresh haemorrhages in the pons and the medulla oblongata) during the last 24 hours of life.

HISTOLOGICAL DESCRIPTION

Microscopical examination showed tumour tissue localized in the pia mater, from which it spread through the cortex along the vessels to the medulla subcortically.

The *leptomeningeal* localization was very widespread and diffuse over the gyri, following the membranes deep into the fissures. The tumour tissue in the meninges resembled that of a spindle-cell sarcoma, as the cells were elongated and somewhat tapering at both ends, but without projecting filaments; they were arranged in bundles, passed in various directions, and might show concentric arrangement around the vessels. There were no pseudorosettes, nor palisade-formations. Fibrillary, slightly fuchsinophil threads were seen intercellularly. Where the tumour tissue had developed freely along the surfaces, lacunar impressions were observed in several parts of the underlying cortical tissue. There were numerous and thin-walled vessels, but hardly any haemorrhages or pigmentation in the meninges.

The growth of the tumour in the *cortex* was in continuity everywhere with the meninges and the subcortical tissue in close relation with the vessels in a peculiar way. The morphology showed an essential change as compared with the appearance in the meninges. In many parts fresh golden brown haemorrhages were seen to the perivascular spaces, surrounded by dark groups of intensely pigmented tumour cells; subcortically the latter became still more conspicuous, showing confluence into dark, connected, and compact tumour masses. In most other areas of the cortex the tumour tissue was paler, almost without pigment, and of a more unripe appearance. The tumour cells contained much protoplasm and were distended, rounded, and in part with less well-defined boundaries. The nuclei were large, pale, slightly polygonal, with conspicuous nucleoli. The protoplasm was rather homogenous, slightly picrinophil or eosinophil. With Cajal-staining, too, the tumour tissue appeared pale, and no fibrils with affinity to gold salts were revealed.

Subcortically, on the other hand, the pigmented tumour cells were predominant, and the perivascular arrangement was exceedingly striking. These tumour cells were rather large, rounded or elongated with round or oval hyperchromatic, dense nuclei, two or three often being superimposed like tiles in each cell. Mitoses were seldom seen. The protoplasm contained numerous fine or coarse blackish brown granules which did not stain with Prussian blue, but whose colour was accentuated by impregnation with silver acording to Fontana's method, and was bleached by hydrogen peroxide. In several parts the pigmented granules were present outside the protoplasm or in the vascular endothelium, which could be clearly distinguished within the tumour cells; the latter, on the other hand, accumulated outside, perivascular. Finally the melanotic pigment was seen in the freely phagocytizing microglia cells, especially in the cerebellum. Haemorrhages were especially seen in relation to the amelanotic tumour tissue, and the golden brown blood pigment was easily distinguished from the blackish brown melanin. Haemorrhages were not infrequently seen without the simultaneous presence of tumour tissue, and were therefore supposed to originate from leakage of vessels in a different section, giving rise to perivascular oozing of blood. In the central part of the medulla no tumour tissue was seen.

In the *thalamus*, tumour tissue was seen along the vessels leading to the nuclei.

The greatest proportion of pigment was seen especially in the *cerebellum* in the form of dark subcortical zones, in which the tumour tissue appeared to be in a resting phase, as the cortex above with its coats of pia was completely normal, smooth, and well preserved. The rounded, tumour-like processes in the posterior part of the cerebellum consisted of confluent tumour isles around the vessels, composed of apparently unripe, pale, and amelanotic tumour tissue in the cortex and the subcortex. Striking features were the pronounced medullary atrophy and the rather well preserved cortex, as there were only slight degenerative changes of the ganglionic cells in the latter.

In the *pons*, partly melanotic tumour tissue was seen anteriorly, invading along the vessels between the pyramidal tract fascicles.

DISCUSSION

The tumour tissue demonstrated was pigmented in the cortex and the subcortex, in many areas in a latent phase with a high content of pigment, in other parts more actively proliferating in a chiefly amelanotic form with a characteristic perivascular arrangement. The meningeal diffuse localization was contributory to the "meningitic" symptoms, as the vessels supplying the cortex were affected, showing stenosis or rupture. The uppermost ganglionic layers of the cortex will therefore be less involved, but anoxia with resulting atrophy will occur in the medullary tissue. The possibility cannot be excluded that the melanotic tumour cells also possess a pronounced oxygen-binding property, as the pigment is able to reduce silver salts, a fact contributing to the same result.

An unsolved problem is the invariable relation of the tumour tissue to the vessels. Is it due to primary, nutritive or evolutionary causes? Or are the tumour processes simply metastatic and localized? Perhaps the progression of the tumour locally will most readily take place perivascularly. There may perhaps be a certain relationship with peritheliomas, developed from the mesodermal tissue. The question of a relationship between the so-called perithelial cell and the congenital melanophores along the vessels in the pia mater must be left unanswered.

How, then, can we explain the relation to the nævi of the skin, which in this case were benign, when the origin of the nævus cells must be considered neuro-ectodermal, whilst at the same time nævi are frequent, possibly constant attendants, as reported in other similar cases. It must be taken for granted that there is actually a connection between nævi of the skin and meningeal melanosis, though metastasizing does not take place. At least it is known that the melaniferous cell has many functions, either as melanophore or melanoblast, or as macrophage in the skin, the pia mater, the retina, and the medulla of the adrenal glands. Therefore, it must also be considered that the origin of the melanin cells is varying, though they are united by the cooperating functions in the melanin metabolism.

With regard to the case reported here it would be natural to assume that it was one of primary intracranial melanoma, both because of the prolonged course without metastasizing which is said to be characteristic of the primary tumours, and because the cerebral symptoms can be dated back almost as early as the congenital nævi of the skin.

In previous publications, the authors often mentioned leptomeningeal melanosis, thus suggesting a primary localization to the meninges of supernumerary, normal melanophores along the pial vessels on a congenital basis (*Willis* (27)). In the present case the melanophores were present intensely, and apparently exclusively, in several areas of the subcortical tissue of the cerebellum. It would therefore be reasonable to suppose that the normal pial and perivascular localization may extend farther through the cortex in cases with an especially great number of melanophores. The primary localization of the tumour developing later will therefore be of minor importance, but the perivascular arrangement will be the main point in the pathogenesis of this tumour.

SUMMARY

A boy, aged six years, with familial predisposition to verrucose nævi developed slight absences and fits of convulsions from the age of two months. When he was five years, he was admitted to an Institute for Speech-Defectives, as he could not speak. During the last three months he had attacks with crying and semiconsciousness. He was admitted to hospital with signs of meningeal affection and changes in the cerebrospinal fluid. There was a regression, but a few days after discharge he had to be readmitted in an acute and moribund state with pneumonia. This was verified at autopsy. The brain as well as the cerebellum presented meningeal and multiple cortical greyish brown foci. There was a large haemorrhage in the left cerebral hemisphere. The pathological changes are compared with the supposed symptoms and with those present clinically. Histological examination showed

melaniferous tumour tissue of somewhat varying morphology. The discussion mentions the perivascular arrangement and the relation to the nævi present in the skin, and, further, the diffuse meningeal spread as the cause of the symptoms resembling those of meningitis.

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A STUDY OF GENERAL PARESIS WITH SPECIAL REFERENCE TO THE REASONS FOR THE ADMISSION OF THESE PATIENTS TO HOSPITAL

By

HARALD FRÖSHAUG and AAGOT YTREHUS

Since the introduction of malarial treatment at the beginning of the 1920es, general paresis research has chiefly been directed towards therapeutic problems. As the present material is the only one of some size published in Norway concerning general paresis, we believe it to be of some interest to give a general account of the material with reference to frequency, sex distribution, age on admission to hospital, incubation period, earlier treatment, occupation, etc. With reference to therapeutic problems, too, it has seemed fitting to trace the development through the years of the conditions under which the patients have been admitted to hospital.

The patients recorded hail from the Psychiatric Department of Oslo City Hospital and Dikemark Mental Hospital, and present quite a representative picture of the frequency of general paresis in Oslo, particularly in recent years, as cases of general paresis without manifest psychotic symptoms are now transferred for treatment to the Psychiatric Department from other hospital departments in Oslo.

In a paper in 1932 from the Psychiatric Clinic, *K. Bendixen* refers to the treatment of general paresis in 90 patients admitted to the clinic from 1926 to 1930, 74 of whom received malarial treatment.

Isberg & Teilmann (1946) published a paper concerning 625 men and 291 women admitted for the first time to Copenhagen city hospitals for general paresis in the years 1925–1941.

E. Lomholt (1931) published a paper concerning 315 male paretics admitted to St. Hans Hospital for the first time 1925–30.

Some of their results are referred to later.

855 patients suffering from general paresis have been admitted to the Psychiatric Department during the 40 years dating from the opening in 1915 to the end of 1954. As some of the patients were re-admitted once or several times, the total number of admissions was 1379.

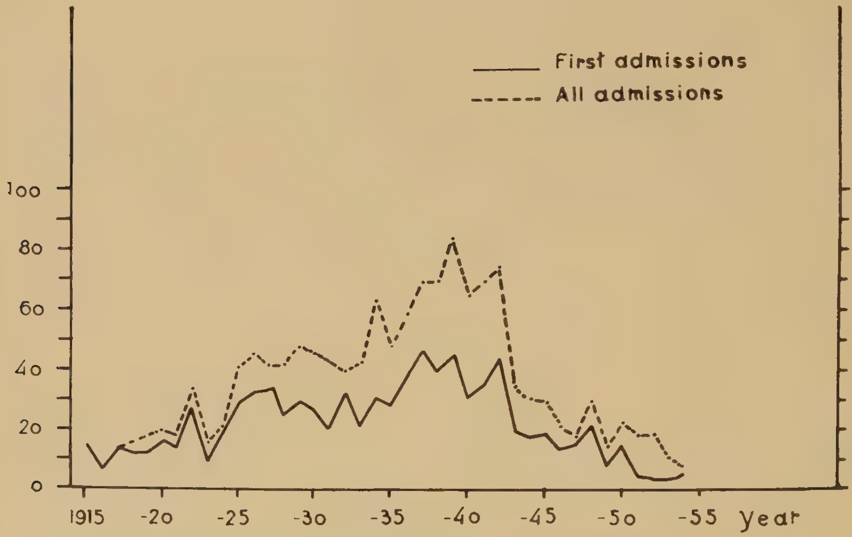

Fig. 1.

Fig. 1 shows that the total number of admissions remained fairly constant from year to year during the first decade, except for a peak in 1922. The average number of first admissions per year was 13.8, and for all admissions 16.6. In this period before the introduction of malarial treatment we must take into account a certain number of cases remaining undiagnosed or drifting into nursing homes, apart from those admitted to the Psychiatric Department.

In the next decade, the curve is at a higher level, but the rise is not uniform. Re-admissions in particular show a considerable rise. The average number per year of first admissions is 27.5, and for all admissions 42.8. This rise is to some extent due to the introduction of malarial treatment in 1923–24. It is probable that these figures also reflect the expansion of the Psychiatric Department, from 58 beds to 126 beds in 1922. The after-control with examination of the cerebrospinal fluid was for some years carried out in the wards and explains the increased number of re-admission cases. Later on these examinations were carried out under out-patient conditions.

In the third decade the numbers of first admissions and total admissions reached a maximum with 46 first admissions in 1937, and 84 admissions in all in1939. From 1942 the numbers are rapidly decreasing. The average number of first admissions in this period is 32.3, and of all admissions 59.8. The remarkable rise in re-admissions, in spite of the strictly observed rule of carrying out the routine control and after-treatment of the patients in the out-patient department, must be associated with the accumulation of more or less imperfectly cured paretics admitted for social-medical reasons.

In the last decade the numbers of both first admissions and total admissions have been slowly decreasing, with an average number of 10.3 first admissions and 18.7 admissions in all per year.

In order to illustrate the relative importance of general paresis in the Psychiatric Department, the number of first admissions of this disease was compared with the corresponding numbers for the two large diagnostic groups of schizophrenia and neurosis. The relative proportion between schizophrenia and general paresis is of special interest during recent years as the diagnostic delimitation of the schizophrenic psychosis has been carried out more consistently than heretofore. As appears from fig. 2, the curves for schizophrenia and general paresis approach each other.

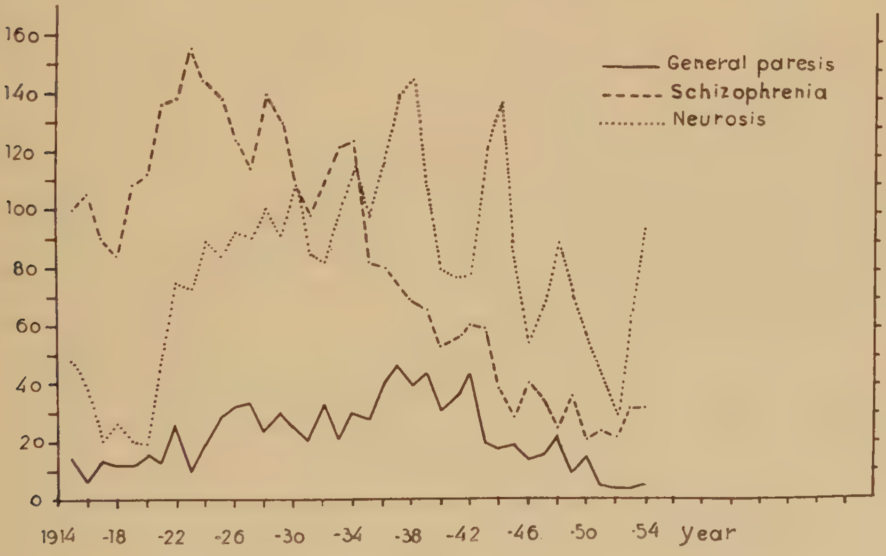

Fig. 2.

The total number of first admissions to hospital of patients suffering from schizophrenia, neurosis, and general paresis 1918–1954.

Is this constantly increasing number of cases of general paresis before the year 1942 indicative of a real increase in the frequency of this disease in Oslo? This is a very difficult question to answer exactly.

The rise is undoubtedly partly due to secondary factors, such as greater diagnostic efficiency of medical practitioners, and the routine serological examinations carried out in hospital departments, which might reveal paretics at an earlier and non-symptomatic stage. These factors, however, cannot be regarded as sufficient to explain the enormous increase, from about 14 cases per year in the first decade, to about 32 cases per year in the fourth decade. In the period under review there has been a rise in the resident population of Oslo, but it does not correspond to the increase in the number of cases of general paresis.

TABLE 1

Year	Resident population in Oslo	Age-group 31-50 years in Oslo	The general paresis rate per 10 000 in the age group 31-50 years
1915	254,775		
1920	260,922	68,783	2.27
1925	255,558	72,686	3.30
1930	256,585	80,107	3.32
1935	269,204	94,080	3.50
1940	271,608	96,128	3.97
1945	286,000	103,612	1.58
1950	435,406	148,401	0.68

As Table 4 shows, about 70 % of the paretics admitted to hospital during the years 1918–1936 belong to the age group 31–50 years. In the same age groups we find a rise on examining the distribution of the population. But if we try to compare the average number of paretics with the number of persons between 31–50 years old, we still find a considerable rise in the number of paretics per 10,000 inhabitants.

It appears to be of some interest to give the numbers of cases of acquired syphilis, notified in Oslo, and first admissions of cases of general paresis in the Psychiatric Department. These numbers are not meant to express the connection between number of cases of acquired syphilis and later development of general paresis, and we have not attempted to draw any conclusion as to the incubation period from these curves, but it is interesting to note how the peak in the curve for general paresis appears about 15 years after the peak in the curve for acquired syphilis, and that the present minimum of general paresis corresponds to a minimum of notified acquired syphilis 15–20 years ago.

Rothström (1930) reports a steady rise since 1923 in the general paresis morbidity in Helsingfors,—a rise demonstrable not only by

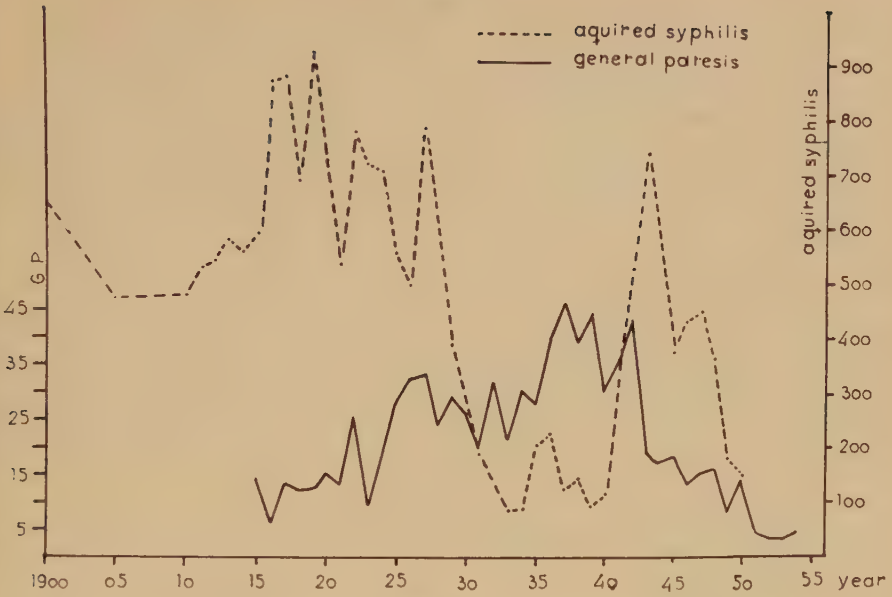

Fig. 3.

The total number of cases of acquired syphilis, notified in the years 1900–1953, and first admissions of cases of general paresis 1914–1954, in Oslo.

comparing the number of paretics with the number of admissions to hospital for mental diseases, but also in relation to the whole population and to the number of persons between the ages of 30 to 50 years.

Wiesel (1923) reports from Stockholm that the number of paretics in relation to the number of the insane, has shown a considerable rise during the period 1911–1923, the rise for male paretics being from 4.6 % to 13.7 %, and for female paretics from 2.2 % to 3.2 %. The number of paretics in relation to the population has also shown a considerable rise during the period 1911–1919.

According to a table published in *M. Lomholt*'s paper of 1944, the admissions for general paresis to St. Hans Hospital and all the Danish

Year	Average number of admissions to St. Hans	Average number of admissions to all Danish mental hospitals
1918–1921	55	91
1922–1925	62	103
1926–1929	70	139
1930–1933	77	163
1934–1937	83	174
1938–1940	65	143

mental hospitals in the period 1918–1940 show a fairly even rise from 1918 to 1937. Afterwards there is a decline.

In Vienna, *Herschmann* (1925), has found a decline in the number of male paretics in the period 1911–1921, and a rise in the number of female paretics. According to *Maier* (1925), the general paresis rate in Switzerland also has shown a tendency to fall.

The present material:

Of the total of 855 patients, *549 belonging to the period 1918–1936 and 1945–54* have been made the subject of a closer investigation. Using these periods we have attempted to make a survey concerning the picture of general paresis before and after the introduction of malarial treatment, and before and after the last world war.

During the first 3 years following the opening of the Psychiatric Department in 1915, the case records were incomplete and not suited for comparison with the records of later years.

All cases of juvenile paresis were excluded, and only those cases of tabo-paresis were included, in which the signs of tabes were completely subordinate to definite signs of general paresis. Wassermann's reaction in serum and cerebro-spinal fluid was the only laboratory test for syphilis up to 1934. Since then the Wassermann test has been supplemented by Kahn and the Meinicke Klärungsreaction II. Furthermore, the cerebro-spinal fluid has been examined with reference to cell counts and proteins, the total protein content as well as the glob.-alb. quotient and the colloidal reactions, first colloidal gold reaction, later the normomastix test. Since 1934 the protein examination has been carried out a.m. Kafka.

The investigation comprises:

1. Sex distribution.
2. Age on admission to hospital.
3. Age on infection.
4. Incubation period.
5. Earlier treatment.
6. The patient's occupation.
7. The clinical classification.
8. The special situation on admission.

The main intention has been to show to what extent the clinical composition of the material has changed in the periods reviewed. We have also tried to ascertain the special symptoms leading to the admission to hospital of this group of patients.

1. *Sex distribution of the material.*

There were 138 women among the 549 patients (25 %), the ratio of women to men being ⅓.

TABLE 2

Years	W/M-ratio
1918–1922	1/4.6
1923–1927	1/3
1928–1932	1/3
1933–1936	1/3.7
1945–1949	1/1.6
1950–1954	1/2.1

Rothström (1930) found a sex ratio of 1/4.44, *Wiesel* (1923) 1/3.7, *Kraepelin* 1/2.5, *Junius & Arndt* (1908) 1/2.35, *Jolly* (1908) 1/3.4, *Bumke* (1936) 1/2.6.

TABLE 3

Sex ratio in the different age groups.

Age on admission	1918-1936	1945-1954
21–30 years	1/2.4	1/1.0
31–40 „	1/4.7	1/2.3
41–50 „	1/3.1	1/2.3
51–60 „	1/2.4	1/2.1
61–70 „	1/6.2	1/1.0
More than 70 years	1/0.3	

TABLE 4

Percentage distribution of the material into age groups.

Age group	21-30	31-40	41-50	51-60	61-70	71-+	Years
Men	3.1	35	36.5	16.8	7.6	0.2	%
Women . .	4.4	24	38	22.5	8.7	3.6	%
Total	3.4	32	36.7	18.2	8	1.1	%

Table 4 shows that most of the patients (68.7 %) were admitted to hospital between the ages of 31 and 50 years. It will also be noted that the age on admission to hospital was higher for women than for men.

Kraepelin and *Bostroem* have arrived at the same result, whereas *Bumke* (1936) found that men were the older on admission to hospital. The average age on admission to hospital was, according to *Kraepelin*, between 35 and 40 years, according to *Bleuler* (1930) between 35 and 45, *Bumke* (1936) 45, *Nonne* (1924) between 36 and 38, *Jolly* (1908) 30–50 years. *Junius & Arndt* (1908) 43 years for men, for women 42 years, *E. Lomholt* (1931) 44.5 years for men, 44 % between 40 and 50 years. *Isberg & Teilmann* (1946) 46.9 years for men, 46.3 years for women, 46.7 years in all. *M. Lomholt* (1944) 44 years.

TABLE 5

Age on admission to hospital.

Age groups	21-30		31-40		41-50		51-60		61-70		71-+		Not known
	M	W	M	W	M	W	M	W	M	W	M	W	
1918			3		6		1	1	1				
1919			2		4	3	2		1				
1920	1		3	1	5	1	1	1	2				
1921			1	1	6	1	3	1					
1922	2		9	1	6	2	2	1	2			1	
1923			1		3	1	1	1	2				
1924			8		9			1					
1925			11	1	7	3	3	1	1			1	
1926	3	2	7	4	8	2	5	1					
1927	1	1	9	3	7	5	3	3	1				
1928	1		11	3	3		2	1	1			1	1
1929		1	10		5	1	4	2	3	2	1		
1930	1		8	2	4	4	6		1				
1931	1		9	2	2	1		3	2				
1932		1	10	3	6	4	5		2	1			
1933			8	1	5	3	2	1	1				
1934	2		8	1	9	3	4	2					1
1935			4		14	3	3	1	2	1			
1936			13	6	9	1	5	2	2				
Total	12	5	135	29	118	38	52	23	24	4	1	3	2
	17		164		156		75		28		4		2
1945			1	1	5	4	5			2			
1946		1	1	1	4	1	1	3	1				
1947					5	1	3	2	2	1		1	
1948			3		8	4		1	1	3		1	
1949			1		3	1	1		2				
1950	1		2	1	3	2	2	1		2			
1951				1	1		2						
1952			1		1		1						
1953					1		1						
1954					1	1	1	1					
Total	1	1	9	4	32	14	17	8	7	8		2	
	2		13		46		25		15		2		

TABLE 6

Average age on admission.

Years	Men	Women	Total
1918–1922	44.7	49.0	45.4
1923–1927	42.5	46.0	44.5
1928–1932	44.0	47.4	45.0
1933–1936	43.7	44.0	43.8
1945–1949	49.5	52.0	50.4
1950–1954	47.8	49.5	48.3

The average age on admission in the whole material is for men 44.6 years, women 47.0 years, in all 45.4 years.

3. *Age on infection.*

43 % of the men and 32 % of the women were able to give information concerning the age on infection. The infection-age was 26.3 years for men, 26.1 years for women. 39 % of the patients were infected between 21 and 25 years, 64 % between 21 and 30 years.

E. Lomholt (1931) found an infection-age of 26 years for men. *Isberg & Teilmann* (1946) found 25.6 years for men, 22.9 years for women. 24.9 years for the material in all.

4. *The incubation period of general paresis.*

It has always for obvious reasons been difficult to obtain correct, if any, information concerning the incubation period. By questioning the patients, by obtaining information from the doctors who have treated them, and by perusing the case records of other departments where the patients have been treated earlier, we have only succeeded in obtaining more or less accurate data concerning the incubation period in 42.3 % of the cases. It is generally assumed that particularly in women the primary stage of the disease escapes notice, and in our material we could determine the incubation period of only 34 % of the female patients, as against 45.5 % of the males.

As previously pointed out, the incubation period in this material was actually longer for women than for men, being 19.7 for women, 15.8 for men, in all 16.7 years.

Bostroem (1930) has found the incubation period to be 17 years, *Wiesel* (1923) 16 years, *E. Lomholt* (1931) 18.3 years, *Bleuler* 17 years, *Kraepelin* between 10 and 15 years, with 3 and 38 years as the extremes in his material. *Fournier* put the incubation period at 10–12 years, with 3 years as the shortest and 24 years as the longest incubation period. The best known study is *Mattauscheck & Pilcz* from 1911. They found that the disease breaks out in most cases between 10 and 16 years after the primary infection, the shortest and longest incubation period, respectively, being 3 and 39 years. As pointed out by *Aebly* (1920) and *Lomholt* (1931), the observation period was too short in this study, being only 10–11 years in certain cases. *Isberg & Teilmann* (1946) found an incubation period of 19.5 years for men, 19 years for women, 19.4 for the material. *M. Lomholt* (1944) found an incubation period of 15 years for men in 1922 and of 21 years in 1935.

In our material there are two patients with an incubation period which appears to be of about two years:

Case 1.

A young woman, A. F., 19 years old, born in 1911, was admitted to the Skin Department of the University Hospital suffering from recent secondary syphilis (no sign of congenital syphilis). Six months later a right-sided hemiparesis developed. Wassermann reaction in blood and cerebro-spinal fluid was positive, the cerebrospinal fluid being normal in other respects. The paresis disappeared after 6 months. In this year she was treated with 11.85 grm. Neosalvarsan and 30.5 cc of a bismuth preparation, Wismol. One year after her discharge from the Skin Department, she was admitted to the Psychiatric Department, suffering from a state of restlessness with delirium of acute onset. In spite of the specific treatment she had latterly received, the examination of the blood and the cerebro-spinal fluid showed general paresis. With malarial treatment partly remission after two months. She was discharged slightly enfeebled, but fully fit for work.

Case 2.

Th. G., a man, born 1905, stated to have been infected Aug. 1944. In Oct. 1944 he developed an exanthema, diagnosed as secondary syphilis. From Nov. 1944 to June 1945 he was treated with 37 injections of Neosalvarsan-Wismol. From 1945 he gradually became more irritable and hot-tempered. 26/12. 1945 he was admitted to the Medical Department with a right-sided hemiparesis. Wassermann reaction positive in blood and cerebro-spinal fluid. Alb.-glob. quotient 0.67, and other changes as seen in general paresis.

According to *S. Lomholt* (1935) secondary syphilis usually becomes manifest 50–70 days after the primary infection.

The longest incubation period, 50 years, was also observed in a woman.

J. E. P., born in 1862, was admitted to a medical department of Ullevål Hospital in 1908. According to her case record she was raped in 1882, and as she was medically examined soon after the rape, the doctor found “that the purification of the blood was not as it should be”. No treatment is recorded. She was married in 1884 and gave birth to 11 children, nine of whom died in infancy. In 1930 she was again admitted to hospital, where her blood gave a positive Wassermann reaction. The cerebro-spinal fluid was not examined. In the same year she had a brief attack of loss of consciousness with transitory hemiparesis and aphasia. Thereupon gradual development of dementia with paranoid features occurred, and in 1932 she was admitted to the Psychiatric Department for the first time, on account of her psychic manifestations and on the initiative of her daughter. On admission blood and cerebro-spinal fluid showed positive Wassermann reaction. In the cerebro-spinal fluid there were 433/3 cells, Pandy +, Weichbrodt ++, colloidal gold reaction 1/2, 2½, 5, 5, 4, 3, 2, 1, 0. Loss of patellar and Achilles reflex. Malarial treatment was followed by considerable improvement, and she returned home. The remarkably long incubation period in this case is a probability, not a proven fact.

Fig. 4 shows that in our material the variations in incubation period showed a wider range than in the study by *Mattauscheck & Pilcz* (1912). As many as 55.5 % of our patients had an incubation period of more than 15 years, while 22.7 % had an incubation period of less than 10 years.

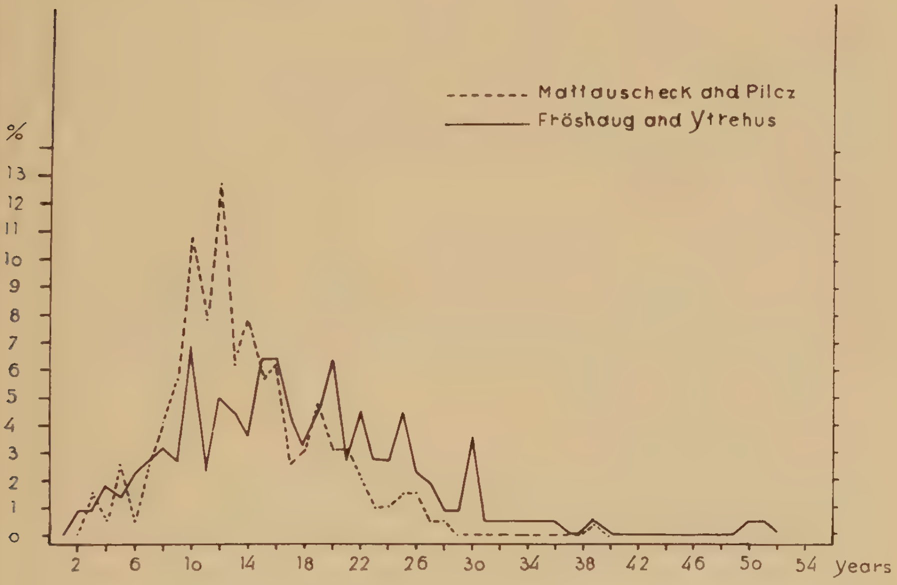

Fig. 4.

Meggendorfer (1921) claims to have shown that the older the patient is at the time of the primary infection, the shorter is the incubation period of the general paresis. Since his investigations were published in 1921, this observation has been confirmed by *Kraepelin & Lange* among others. A similar condition was found in our material. *Meggendorfer* states that when a primary infection occurs between the ages of 16 and 20 years, the average incubation period is 17.2 years, whereas it is 8.7 years when the infection has occurred between the ages of 41 and 45.

In our material there also is a shortening of the incubation period with rising age. This observation can possibly to some extent be explained by the increasing mortality rate with older age, which again entails that with increasing infection age more people die before developing general paresis. (*Isberg & Teilmann* 1946).

TABLE 7

Infection age and incubation period.

Years	Fröshaug & Ytrehus	Bumke	Meggendorfer	Jørg., Neel. Schrøder	E. Lomholt	Isberg & Teilmann
16–20	20.5	20.2	19.5	22.3	22.5	22.8
21–25	19.2	17.7	15.6	16.8	18.6	20.6
26–30	15.5	14.6	13.2	16.9	17.7	18.2
31–35	15.4	12.2	11.4	15.5	14.8	19.0
36–40	10.8	11.6	10.1	12.9		15.6
41–45	12.4	11.5		12.9		13.4
46–50				11.5		

5. *Earlier treatment.*

It is as difficult to obtain reliable data concerning the treatment a patient has received in the primary and secondary stages of the disease as it is to determine the incubation period. The information supplied by the patients themselves is often incomplete and difficult to verify. The present material is therefore little suited to demonstrate the effect of anti-syphilitic treatment on the appearance or development of general paresis.

It may be said, with the necessary reservations, that of 549 patients 147 had received some treatment. In most cases this treatment had been quite unsatisfactory, both as compared with the treatment used at the time of infection and present-day treatment. This is largely due to the lack of or inadequate follow-ups of the patients. Only in 13 cases does the treatment appear to have been adequate. *M. Lomholt* (1944) found in her study of 686 patients that “there was no information concerning a single patient who had received anti-syphilitic treatment fulfilling modern requirements.”

6. *The patients’ occupation.*

Among the 412 men in the present material there are 398 about whom reliable information was obtained concerning their occupations. The largest group consisted of skilled labourers and not independent artisans, a total of 115, or 31 % of all the men. 79 patients, or 19.7 % of all the men, were unskilled labourers – dock workers, day-labourers, etc. An equally large group (80 patients) consisted of employees, shop assistants, cashiers, book-keepers, office personnel, and subordinate State officials. The higher social level consisting of independent business men, independent artisans, higher employees, administrators, etc., was represented by 56 patients, or 14 %. Sailors ranging from captains to seamen numbered 42 patients, or 10 %. The smallest group of 15 patients, or 3.8 %, belonged to the so-called liberal professions,—doctors, lawyers, artists, and journalists.

Among the 138 women the character of their occupations was stated in 121 cases. 45 patients, or 38 %, were unmarried. 8 of them were office workers, 10 worked at home (sewing, etc.), and 5 were charwomen. Domestic servants formed the largest group among the unmarried, a total of 21. One of the woman can only be considered a vagrant.

The married women totalled 76. The largest group, 30 patients, consisted of wives of unskilled labourers. 18 were married to artisans, 16 to employees, 6 were self-supporting women, one had been married to a sailor, and 5 belonged to the upper social classes.

7. *The clinical classification of the material.*

The conventional classification according to the clinical manifestations of general paresis has in the main been followed here.

1. *Initial paresis.*

Included under the heading of initial paresis are the cases which present various neurasthenia-like manifestations of a non-specific character, but which on closer analysis reveal a slightly reduced power of imprinting, a defective capacity on the part of the patient to judge his own condition, and a hint of emotional instability.

For practical reasons the cases have also been included in this group in which a neuro-psychiatric examination failed to show definite signs of general paresis, but in which the examination of the blood and cerebro-spinal fluid showed characteristic signs of this disease (positive humoral syndrome). In this way, initial paresis came to constitute about 12 % of all the cases (65 out of 549 cases).

2. *Mainly demential syndromes.*

This group includes all the cases in which the most prominent manifestations were of a demential character. First and foremost, there

TABLE 8

Year	Initial paresis	Demential	Classical megaloman	Attacks of paresis	Stuporous delirious	Schizophreniform	Total
1918		7	2		1	2	12
1919		7	2		1	1	11 + 1 u.k.
1920		11		3		1	15
1921		7	1	3		2	13
1922	3	7	3	8	3	2	26
1923		5	1	1		2	9
1924		9	1	5	3		18
1925	3	13	3	4	4	1	28
1926	5	15	3	1	7	1	32
1927	1	18	2	4	4	4	33
1928		13	1	3	5	2	24
1929	4	11	3	6	3	2	29
1930	3	15	3	2	1	2	26
1931	1	8	3	2		6	20
1932	5	17	1	4	4	1	32
1933	4	5	1	6	2	3	21
1934	5	14	3	3	2	3	30
1935	5	8	2	6	5	2	28
1936	4	22	1	9	2		38
1945	2	13	1	1	1		18
1946	2	5		4	1	1	13
1947	5	6	1	1		2	15
1948	5	8	1	4		3	21
1949	2	5				1	8
1950	5	8		1			14
1951	1			2		1	4
1952		3					3
1953		1		1	1		3
1954		3				1	4
In all	65	264	39	84	50	46	549
Per cent	11.8	48.0	7.1	15.3	9.1	8.4	

were all the cases of simple dementia, followed by the demential states with an element of euphoria, and the rare types with depressive colouring of the clinical picture. Common to all these cases was the steadily progressive mental deterioration. This, the largest group, included 264 cases, or 48 % of the total.

3. *Classical megalomaniacal general paresis.*

As will be explained more fully further on, the total number of cases in this category was very small, i.e. 39, or about 7.3 %.

4. *Attacks of paresis.*

The cases primarily characterized by apoplectiform and epileptiform attacks proved to be twice as numerous as the cases of the classical form, numbering 84, or 15.3 % of the total.

5. *Stuporous-delirious paresis.*

The clinical picture in this group is characterized by confusion with loss of orientation, anxiety, to some extent delirious-amential syndromes with increased psychomotor activity or stupor. The 50 patients in this group constituted 9.1 % of the total.

6. *Schizophreniform cases.*

This group includes all the cases of general paresis with a schizophreniform symptomatology, all the demential-paranoid cases and those presenting hallucinations of a more chronic character. These psychoses are not uncommon in our material, and are more numerous than the classical megalomaniacal cases—46 cases, or 8.4 % of the total.

When we are confronted with a schizophrenia-like clinical picture, there is always the possibility that we are dealing with schizophrenia and general paresis occurring at the same time. It is beyond the scope of these investigations to discuss the ability of general paresis to excite a schizophrenia hitherto running a latent course. The situation, however, is comparatively clear in the following case:

E. M. J., born 1882, dock labourer, was treated in the Psychiatric Department in 1927. It was stated on admission that between 1906 and 1909 he had been an inmate of Dikemark Mental Hospital suffering from a schizophrenic psychosis. After being discharged, he married, and his wife stated that he had always been rather obstinate and fussy, but had otherwise presented no psycho-pathological features till five weeks before admission to the Psychiatric Department. He then began to suffer from hallucinations without clouding of consciousness—he felt he was under observation and was not allowed to walk the streets in peace by trams and motor-cars. He believed he was himself a loud-speaker. Now and then he presented definite katatonic traits. On admision to hospital he presented some degree of dementia with reduced powers of concentration. There was incomplete absolute rigidity of the pupils. Serum: WaR ++. Cerebro-spinal fluid: WaR 0.50 + , 1.0 weak +, 35/3 cells. Nonne + (+). Weichbrodt +++. T. A. R. +++. Colloidal gold reaction: paralysis curve: 5-5-5-5-5-5-5-3-0-0. He was given malarial treatment and there was some improvement. He continued to suffer from hallucinations after his discharge, and in Nov. 1927 was readmitted to Dikemark Mental Hospital, from where he was transferred in 1936 to a private home. There was no history of syphilis in this case.

This was undoubtedly a case of schizophrenia in a patient who, before or after the manifestation of this disease, contracted syphilis and developed general paresis. (The patient's age at the time of the outbreak of the general paresis presumably excludes the diagnosis of congenital syphilis with juvenile general paresis.)

In some cases the symptoms may be so characteristic of schizophrenia that the signs of general paresis detected in the cerebro-spinal fluid come as a great surprise. The diagnostic problems become particularly complicated when, a long time after a course of malaria and after the cerebro-spinal fluid and blood have been restored to normal conditions in respect of syphilis, we are again confronted by the appearance of a psychosis more or less suggestive of schizophrenia. These problems are illustrated by the following case:

J. C. N., born 1874. Masseuse. She was treated in the Psychiatric Department 1927–1928. A sister and a nephew suffered from schizophrenic psychoses. She herself had always been sensitive and touchy. Eight years before admission to hospital she lost her job in a shop on account of some peccadillo. She was much upset by the dismissal and became more touchy than ever. Her new occupation as masseuse troubled her much, because she was always afraid of hurting her patients. A paranoid psychosis with hallucinations and of a definitely schizophrenic character developed gradually. She heard voices and experienced magnetic currents, and noticed that her thoughts were "taken from her." All strength was sucked out of her, and she "was driven to do strange things."

On admission to hospital she behaved sensibly and disclosed no actual dementia. But she was much engrossed by her paranoid ideas and was somewhat depressed. A neurological examination proved negative. The cerebro-spinal fluid: 22/3 cells, Nonne ++, Weichbrodt +++, WaR 0.10 +. Colloidal gold reaction: complete precipitation in all the glasses. WaR in the serum ++.

The paranoid manifestations with hallucinations disappeared directly after the malarial treatment, and her behaviour was quite sensible except for slight manifestations of euphoria. She was given after-treatment with tryparsamid, a total of 55 injections, each of 3 grm. The cerebro-spinal fluid responded well to this treatment. In July 1929 an examination of the cerebro-spinal fluid showed 1/3 cells, glob. 4.8 mg.%, alb. 40.8 mg.%. Colloidal gold reaction: moderate secondary type. WaR —, Serum WaR —.

The paranoid psychosis with hallucinations recurred in Oct. 1933. Some months before this she had had vague paranoid ideas, had felt herself the object of gossip and slander, and had gradually developed lively hallucinations. On admission to the Psychiatric Department in Oct. 1933 she showed no pathological change in the serum and cerebro-spinal fluid. She was transferred to Dikemark Mental Hospital, from where she was discharged as symptom-free after three months. A renewed examination of the blood and cerebro-spinal fluid showed normal conditions.

A third case will be referred too, to show the difficulty of making the differential diagnoses schizophrenia—general paresis.

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S. T., a woman born 1907. During pregnancy 15 years old treated with "some injections". The child was still-born. Later she was married twice, had one living child and no abortions. She was treated with some injections during her second pregnancy, too.

During treatment for thrombophlebitis 1952 her doctor found that Wassermann reaction in blood was positive, but she received no specific treatment.

From 1952 she became nervous, made several mistakes while working. From Dec. 1953 she was reported ill. She behaved in a strange way, suffered from paranoid ideas, said and did strange things.

In March 1954 she got 2 ECT. After the second ECT she became apathetic, refused to eat, was dizzy. Neurological examination showed anisocoria, with no reaction to light. There was amentia for the period after her first ECT. Further examination showed WaR —, Kahn —, MKR (+) in serum, 8/3 cells, WaR + (titre 21), MKR +++ in cerebro-spinal fluid. After malarial treatment discharged to her home.

To show how the conditions on admission have changed during the period examined, the cases have been divided into six groups, five of five years and one of four years.

TABLE 9

The percentage distribution of the sub-groups of general paresis in the various periods.

Year	Initial paresis	Demential	Classical megalo-man.	Attacks of paresis	Stupor. delir.	Schizo-phreni-form
1918–22	3.8 %	50.0 %	10.3 %	18.0 %	5.1 %	10.3 %
1923–27	7.5 „	50.0 „	8.3 „	12.5 „	15.0 „	6.7 „
1928–32	10.0 „	48.8 „	8.5 „	13.0 „	10.0 „	10.0 „
1933–36	15.9 „	41.8 „	6.0 „	20.0 „	9.4 „	6.8 „
1945–49	21.4 „	49.4 „	4.0 „	13.3 „	2.7 „	9.2 „
1950–54	21.4 „	53.4 „		14.3 „	3.8 „	7.1 „

During the first five years there were only three out of 78 patients (3.8 %) who belonged to the group initial paresis. Thereafter there has been a gradual and remarkably uniform and definite rise in this group. The classical, megalomaniacal form of the disease shows a dwindling frequency, from 10.3 % in the first five-years group to none in the last group. There is no special change in the relative frequency of the other forms of the disease.

It seems to us that this grouping by periods is instructive. Surely, a total cross-section of the material does not show us any important departure from that recorded by other investigators. But a direct comparison presents difficulties for want of uniformity of classification by the various authors. Attention will in peculiar be drawn to the rarity of the classical form of general paresis. In our material it reached a maximum of 10 %, whereas *Meggendorfer* (1921) puts its frequency at 15–20 %. But *Bostroem* has found it in 10 %. In his material from the Norwegian University Clinic, *Bendixen* (1932) found megalomania in 20 out of 63 cases, a far higher rate for the classical form than in our material.

It has earlier been pointed out, by *Pilcz* (1908) among others, that this classical form is gradually becoming rare. This seems to be confirmed by the present material, but has not been observed by *M. Lomholt* (1944).

8. *The special admission-situation.*

It is more interesting to analyse the relation between the symptoms and the reaction of the patients' associates upon them than to study the clinical symptoms isolatedly. We have therefore been interested in establishing the circumstances causing our patients to be admitted to a psychiatric department. In this connection we have also desired to find out whether the patients have gradually been taken care of at an earlier stage of the disease.

To answer these questions, it has been necessary to undertake a new classification of the material based on the main reasons determining the patients' admission to hospital.

TABLE 10

Reasons for admission to hospital.

I. *At own request*		109 pat.
a. Patients conscious of being ill	101	
b. Patients who sought medical advice because of psychotic reactions	8	
II. *Patients admitted on the initiative of others*		323
a. Social deterioration	178	
b. Specially alarming psychic and somatic manifestations	142	
c. Environment control + routine control	3	
		432
III. *Inadequate reports of the situation on admission*		117
		549 pat.

I. *At own request.*

Altogether 109 patients, or 25.5 % of all the patients whose situation on admission is known, sought medical advice on their own initiative. In the course of time there has been a considerable rise in the number of such patients.

TABLE 11

Patients admitted at their own request 1918–1936 and 1945–1954.

Year	Total admitted	Those with known situation on admission	Own request	Percentage
1918–1922	78	53	3	5.6
1923–1927	120	102	15	14.7
1928–1932	131	110	34	30.9
1933–1936	117	94	33	35.0
1945–1949	75	52	18	34.5
1950–1954	28	22	6	27.4

In connection with this rise we must note the general tendency to seek medical advice early, the greater number of doctors in a large town, the development of sickness insurance and other factors.

It would appear from the case records that 75 patients sought medical advice for symptoms directly associated with general paresis.

16 patients presented neurological manifestations, such as hemiparesis, disturbances of gait and co-ordination, and dysarthria. In 11 cases, very marked headache and giddiness made the patients' admission necessary. In 38 cases, slight psychic disturbances were the determining factors. As a rule, such neurasthenic symptoms as irritability, slight depression, early failure of the memory, distraction sensations, disinclination to work, etc., were the conditions which the patients themselves interpreted as signs of disease. Although in many of these cases the disease had already progressed so far that it could not be included in the group of initial paresis, these patients were so conscious of being ill that they themselves took the initiative of seeking medical aid.

In 9 cases the psychotic manifestations were so dominating and had reached such a pitch that the patients could be certified as insane. These patients had sought medical aid for protection against imaginary persecution, with the exception of one of them, a very intelligent man, who, whilst still in the throes of an attack of megalomania, yet realized that something was wrong with him and sought medical aid on his own initiative.

35 patients sought medical aid for physical ills not due to the general paresis. Several of these patients were transferred from other hospital departments. These transfers will be dealt with below.

The average duration of symptoms before admission to the Psychiatric Department was shorter for the patients seeking medical aid on their own initiative than for all the patients. Owing to the very nature of general paresis it is quite impossible to obtain reliable data concerning the duration of symptoms in the cases with insidious onset of the disease. But we hope that it has been possible to obtain approximately accurate information concerning the duration of symptoms.

TABLE 12

Duration of symptoms before admission of patients coming to hospital on their own initiative.

Years	1 month	1-3 months	4-6 months	7-12 months	1-2 years	2 years	Unknown
1918–1922		1	1		1		
1923–1927	3	2	4	2	1	1	2
1928–1932	11	6	4	3	6	1	3
1933–1936	6	4	8	11	2		
1945–1949	3	4	8	1			2
1950–1954	3		1			1	1

TABLE 13

Average duration of symptoms before admission to hospital.

Years	All the patients	Patients admitted at own request	Patients with social deterioration	Patients with particularly alarming psychic and somatic manifestations
1918–1922	13 months		14 months	11.5 months
1923–1927	9 „	8	13 „	9 „
1928–1932	8 „	7	10 „	7 „
1933–1936	8.8 „	6.8	7 „	14 „
1945–1949	9 „	3.9	10 „	9.3 „
1950–1954	7.9 „	6.2	7.4 „	7 „

II. *Cases in which the initiative for admission to hospital was taken by others than the patient.*

These patients formed the largest group, with 323 patients, or 75 % of all the patients where the situation on admission to hospital is known. In these cases the paretic process had matured to such an extent that its manifestations could no longer be misinterpreted by the relatives as “overwork” or “nerves”.

a. *Social deterioration.*

Among the 323 cases 178 were in a special category. Here we find the clinically familiar and characteristic cases of slowly progressive mental deterioration without a sense of illness. In such cases there necessarily comes a time when the patient and his relatives clash on their conception of what is right and proper.

Among these 178 patients are 34 whose admission to hospital was necessitated by excessive irritability and emotional instability culminating in violent scenes of jealousy and threatening behaviour in and outside the home, acts of aggression and attempts of suicide in moments of anger. In most cases it was the husband or wife who took the necessary steps to secure admission to hospital, but it also occasionally occurred that the police or other authorities had to take action.

In only 13 cases there were definite criminal lapses, petty burglaries, elementary swindling, theft, vagrancy, etc. Most of these patients had been arrested and their behaviour towards the police was so curious that they were admitted to hospital for observation.

In 21 cases there was a record of unseemly behaviour, ill-fitted to the occasion, in the home or at the place of work, striking breaches of good behaviour, an incorrigible urge to gamble, etc.

In 110 cases, admissions to hospital were due to less dramatic situations, the gradual manifestation of incapability, inability to work, muddling, and debility.

TABLE 14

Patients admitted on the initiative of others.

Admission on the initiative of	Patients with social lapses	Patients with particularly alarming psychic and somatic manifestations
Husband or wife	75	54
Some other near relative	48	48
Guardian, boarding-house manager, neighbour, employer	28	20
The police	27	20
In all	178	142

The grouping of the patients in periods of so many years shows that social lapses have become less frequent. A constantly growing proportion of the patients is admitted to hospital before they have a chance to display the grosser manifestations of the disease. In this connection one must remember the small numbers of the last period which makes the comparison more difficult.

TABLE 15
Social lapses.

Years	Social lapses	Percentage of the admissions in which the situation on admission was known
1918–1922	29 patients	55.8
1923–1927	45 „	44.1
1928–1932	41 „	37.3
1933–1936	32 „	34.0
1945–1949	22 „	42.3
1950–1954	9 „	41.0

TABLE 16
The duration of symptoms before admission of patients with social lapses.

Years	1 month	1-3 months	4-6 months	7-12 months	1-2 years	2 years	Un-known
1918–1922	1	2	7	9	4	6	1
1923–1927		5	12	9	11	3	5
1928–1932	2	12	7	7	8	1	4
1933–1936		7	9	9	3		4
1945–1949	1	1	7	8	2	3	
1950–1954	1	1	2	4			1

b. *Particularly alarming psychic and somatic manifestations.*

In 142 cases the patients' relations were alarmed by the acute onset of grave symptoms such as attacks of paresis, megalomania, delirium, and psychoses presenting a schizophreniform picture. These manifestations are enough to account for the admission to hospital. In many

TABLE 17
The duration of symptoms before admission of patients with particularly alarming psychic and somatic manifestations.

Years	1 month	1-3 months	4-6 months	7-12 months	1-2 years	2 years	Un-known
1918–1922	3	1	1	6	5		4
1923–1926	12	14	5	2	4	1	4
1927–1932	11	6	2	5	6		5
1933–1936	6	2	8	2	3	3	3
1945–1949	1	1	2	3	1	1	2
1950–1954	2	–	2	–	2	–	1

cases these acute phenomena were the first clinical manifestations of general paresis. This was particularly so in the cases of megalomania. But in other cases, the first indications of the disease may be traced very far back in time, and in the course of years there is no positive reduction in the average duration of the symptoms before admission to hospital.

TABLE 18

Patients with particularly alarming psychic and somatic manifestations.

Years	Alarming psychic and somatic manifestations	Percentages of admissions with known situation at the time of admission
1918–1922	20 patients	38.5
1923–1927	42 ,,	41.2
1928–1932	35 ,,	31.8
1933–1936	37 ,,	28.7
1945–1949	11 ,,	21.0
1950–1954	7 ,,	32.0

Transfers from other hospital departments.

Among the 549 patients 129 were first admitted to other hospital departments. The reason was attacks of paresis in 31 cases. In 51 cases, general paresis was diagnosed with comparative ease because of the clinical picture, and in the remaining 47 cases the manifestations of disease for which the patients were admitted to hospital had nothing to do with general paresis.

The value of a routine control and examination of the cerebrospinal fluid of seropositive cases is shown by the fact that in this way general paresis came to be discovered and to receive early treatment in 47 cases.

TABLE 19

Transfers from other hospital departments.

Years	All admissions	Transfers	Percentage
1918–1922	78	6	7.0
1923–1927	120	14	11.0
1928–1932	131	32	24.4
1933–1936	117	22	20.0
1945–1949	75	41	55.0
1950–1954	28	14	50.7

c. *Environment control and routine control (not in hospital).*

The routine examination of the husbands, wives and children of general paresis patients has not only led to the detection of a certain number of cases of congenital syphilis, but has also revealed three cases of general paresis, two of them belonging to the period 1933 1936. One of these patients was clinically symptom-free, but with a cerebro-spinal fluid characteristic of general paresis. The other patient proved on closer examination to show signs of incipient dementia.

The third patient was a sailor who, when examined on returning to Norway in 1945, showed a cerebro-spinal fluid characteristic of general paresis.

CONCLUDING REMARKS

The periods under review, 1918–1936 and 1945–1954, reveal definite changes in the situation on admission to hospital of general paresis patients. This change is first and foremost shown as a uniform rise in the number of cases recommended for treatment at an early stage, before the paretic process has been able to inflict serious damage on the patient's psychic equipment.

At the same time we have been able to show that the duration of symptoms before admission to hospital has become shorter, not only for the patients who seek medical aid themselves, but also for those who are directed to medical aid by others.

The reasons for this satisfactory trend are numerous. What is undoubtedly of importance is the constantly growing complexity of human civilization, which does not tolerate any marked departure from the normal and accepted behaviour.

With the present organisation of the public health service without a planned, far-sighted system of control of the notified cases of primary syphilis, it is doubtful if such patients as those who betray themselves by social lapses will be able to receive treatment much earlier than they do at the present time. Even in the most highly differentiated environments the reaction to early psychic manifestations will be somewhat delayed.

SUMMARY

1. A study has been made of general paresis at the Psychiatric Department of the Oslo City Hospital (Ullevål) and Dikemark Mental Hospital. The material consists of 855 patients, admitted from Jan. 1, 1915, to Dec. 31, 1954. The material is supposed to be approximately representative of the city of Oslo.

2. In the first decade there was an average of about 14 admissions of new cases per year. In the two following decades the average number was 27.5, respectively 32.3 per year. In the last decade the average was 10.3 first admissions per year. There has been a similar tendency concerning readmissions.

3. The 549 patients admitted for the first time in 1918–1936 and 1945–1954, 29 years, have been made the subject of further studies.

4. The ratio of women to men was 1/3.

5. The patients admitted to hospital between 31–50 years of age constituted 68.7 % of the total material. The average age on admission was 45.4 years. (M: 44.6 W: 47.0).

6. The average age on infection was 26.2 years.

7. The average incubation period was 16.7 years, for women: 19.7, for men: 15.8.

8. Only 13 patients had received an anti-syphilitic treatment that could be considered adequate.

9. Skilled labourers and non-independent artisans formed the largest group of male patients, with 31 % of the total. Unskilled labourers constituted 19.7 %. An equally large group was formed by subordinate employees. The higher social level was represented by 14 % of the total, the so-called liberal professions by 3.8 % and sailors by 10 %. 38 of the female patients were unmarried.

10. There was a uniform rise in the number of patients with initial paresis, and a decline in the number of classical megalomaniacal cases. Initial paresis constituted 11.8 % of the total, demential form 48 %, classical megalomaniacal form 7.1 %, attacks of paralysis 15.3 %, stuporous-delirious 9.1 %, and schizophreniform 8.4 %.

11. 25.4 % of the patients with known situation on admission sought aid on their own initiative. This group has increased. Social lapses were responsible for the admission in 41.5 %. The number of these cases has decreased.

12. The duration of symptoms before admission to hospital has shown a uniform shortening, both for the patients seeking medical aid on their own initiative and for the patients committing social lapses.

13. 33 % of the patients were admitted because of particularly alarming psychic and somatic manifestations.

14. 23.5 % of the patients were transferred from other hospital departments. 36 % of these patients were discovered because of the routine serum control and examination of the cerebro-spinal fluid of seropositive cases.

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EXPERIMENTS IN THE PROLONGATION OF CONVULSIONS INDUCED BY ELECTRIC SHOCK TREATMENT

By

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The duration of an induced epileptic seizure in man, if the first shock in a series of treatments is excluded, is, on an average, 38 seconds (*Holmberg* 1954 a). The first treatment in a series gives rise to a longer seizure, about 3–6 seconds longer than the subsequent seizures (*Holmberg* 1954 b). The administration of oxygen immediately before treatment prolongs the duration of the seizure by some seconds (*Holmberg* 1953). *Altschule & Tillotson* (1947) have pointed out that curarization prolongs the duration of the seizure by approximately one third. When a routine dose of succinylcholine iodide is administered as a muscle relaxant together with the inhalation of oxygen, the duration of the seizure is often increased considerably; a seizure lasting 2 min. 30 sec. has even been observed (*Holmberg & Thesleff* 1951). The prolongation of the duration of the seizure is usually particularly pronounced in the first treatment of a series (*Holmberg* 1954 b). When there was total muscular relaxation and continuous insufflation of oxygen a seizure lasting 5 min. 53 sec. has even been observed (*Holmberg* 1953). *Ruf* (1951) found that in animals a seizure could be prolonged up to 1½ hours by administering oxygen and large quantities of adrenalin. This was attributed to the fact that both hemispheres function alternately, which is not the case in human beings.

It has been our purpose to investigate more closely to what extent the duration of a seizure induced by electric shock treatment may be prolonged, on the one hand, by the administration both of a muscle relaxant and oxygen, and on the other hand, by carrying out experiments with certain stimulants.

I. *The duration of the convulsions in routine administration of a muscle relaxant and inhalation of oxygen.*

150 electric shock treatments where a routine dose of muscle relaxant was administered (slow intravenous injection of succinylcholine iodide 0.25–0.30 mg/kg body weight, mixed with Evipan 0.15–0.20 g., and the simultaneous inhalation of oxygen, see *Holmberg & Thesleff* 1952) were compared with 329 unmodified treatments (only a few breaths of oxygen). The duration of the convulsions was timed with a stop watch. Only the first treatment in a series was used for purposes of calculation.

For the unmodified treatments the duration of the convulsions was 48.7 ± 0.52 seconds, and when muscle relaxants were employed the duration was 71.9 ± 1.95 seconds. The difference (23.2 seconds) was highly significant; $t = 11.52$, $df = 477$ and $P < 0.001$.

II. *The duration of the convulsions with total muscular relaxation and insufflation of oxygen.*

Electric shock treatment was administered to 26 patients under conditions of total muscular relaxation (first thiopental sodium 0.20–0.25 g., then succinylcholine iodide 0.08–0.10 g.) and continuous manual insufflation of oxygen. The convulsions were recorded electroencephalographically. In one case the duration of the convulsions was nearly 6 minutes (353 sec.), in 2 cases it was over 4 minutes (278 sec. and 255 sec., respectively), in 2 cases over 3 minutes (221 sec. and 196 sec., respectively, in 2 cases over 2 minutes (127 sec. and 123 sec., respectively), in 5 cases over 1½ minutes, in 12 cases over 1 minute, and only in 2 cases was it less than 1 minute. The average duration of the convulsions for the 26 patients was 114.5 seconds. If only the 12 cases are taken into consideration where either one (routine and unmodified) or no electric shock treatment had been previously administered, the duration of the convulsions was 162.0 ± 27.55 seconds.

On comparison with treatments where a routine dose of muscle relaxant (part I) was administered, the difference was significant; $t = 3.262$, $df = 160$ and $P = < 0.01$.

III. *Experiments with intravenous infusion of nor-adrenalin before and during the seizure.*

In 6 cases the effect was tested of a l-nor-adrenalin infusion, 0.125–0.25 microgram/kg/min., during the whole seizure. The infusion was started 2–3 minutes prior to the electric shock and simultaneously with the administration of the muscle-relaxant treatment (the same technique was employed as in part II). The seizure was recorded electro-

TABLE 1

Effect of intravenous infusion of nor-adrenalin on duration of convulsions, blood pressure, and heart frequency.

Subject	Nor-adr. γ/kg/min	Increase in blood pressure before shock, mm.	Duration of convulsions seconds			Max. systol. blood pressure, mm. Hg		Max. heart frequency/min.	
			Control	Nor-adr.	Diff.	Control	Nor-adr.	Control	Nor-adr.
G-n ♀	0.25	45	55	77	+22	175	205	113	112
W-h ♀	0.25	–	68	100	+32	–	–	95	124
W-r ♀	0.25	25	66	77	+11	175	200	162	146
B-n ♀	0.20	30	131	86	—45	170	185	152	120
L-m ♀	0.15	15	63	70	+ 7	185	190	143	143
L-ö ♀	0.125	25	34	41	+ 7	230	270	106	147

encephalographically, ECG was taken from the arms, and the blood pressure was measured by auscultation every 30 seconds.

The results are shown in *Table 1*. In 5 cases the duration of the seizure was somewhat prolonged, in 1 case it was shorter when nor-adrenalin was administered. The blood pressure was higher throughout, but the heart frequency was, as a rule, lower, which are typical effects of nor-adrenalin. None of the differences was significant.

By way of contrast, an experiment will be mentioned that was carried out with amyl nitrite, a substance that has the effect of dilating the blood vessels and lowering the blood pressure; in other respects the treatments were unmodified. A few drops were given by means of inhalation immediately prior to the shock, which caused a facial flush. The duration of the seizure was timed with a stop watch.—The results are given in *Table 2*. In every case in which amyl nitrite was administered the duration of the seizure was shorter than in the control experiments. The average for the amyl nitrite experiments was 36.0 seconds, and for the control experiments (the mean of the means for every control pair) was 46.9 seconds. The differences of 10.9 ± 2.85 seconds was nearly significant; $t = 3.827$, $df = 4$ and $P < 0.05$.

TABLE 2

Effect of amyl nitrite on duration of convulsions.

Subject	Duration of convulsions in seconds		
	Control before	Amyl nitrite	Control after
S-r ♀	45	40	49
A-m ♀	30	26	36
N-n ♂	50	38	42
T-s ♂	63	48	54
G-r ♀	52	28	48

TABLE 3

Effect of intravenous injection of Metrazol on duration of convulsions, blood pressure and heart frequency.

Subject	Metrazol, ml.	Duration of convulsions seconds			Max. systol. blood pressure, mm. Hg		Max. heart frequency/min.	
		Control	Metrazol	Diff.	Control	Metrazol	Control	Metrazol
C-a ♀	3	62	69	+ 7	190	210	146	156
H-t ♂	3	80	78	— 2	210	–	154	160
F-n ♂	3	92	94	+ 2	250	–	180	156
Ö-d ♀	12	49	71	+ 22	210	250	150	154
E-n ♂	12	114	196	+ 82	200	230	162	172
F-n ♂	10	64	110	+ 46	220	220	165	172
K-n ♀	8[1]	56	90	+ 34	230	250	170	184
H-m ♂	9[1]	98	224	+126	200	215	182	172
H-t ♂	10[1]	100	128	+ 28	210	220	156	174
F-n ♂	9[1]	64	124	+ 60	220	240	165	165

[1] In these 4 cases a seizure was induced by Metrazol alone.

IV. *Experiments with intravenous injection of Metrazol prior to the seizure.*

In connection with electric shock treatment where there was total muscular relaxation (same technique as in part II) in 10 cases a 10 per cent solution of Metrazol was quickly injected intravenously. When the drug did not induce a seizure, this was brought about by an electric shock after approximately 1 minute. The seizure was recorded electroencephalographically. The heart frequency was measured by means of ECG, and the blood pressure was determined by auscultation every 30 seconds.—It was frequently found that even large doses of Metrazol (10–12 ml) failed to induce a seizure. This is probably due to the fact that it was necessary to administer barbiturates in order to prevent discomfort when the muscles were relaxed. A seizure was invariably induced on the administration of an electric shock.

The results are shown in *Table 3*. A small dose of 3 ml Metrazol-solution apparently had only an insignificant effect on the convulsions. A larger dose, 8–12 ml., exerted a more marked effect. When the Metrazol alone induced a seizure, the duration of the convulsion was the longest observed for the individual concerned. The convulsions were prolonged significantly by means of the large doses of Metrazol by 56.9 ± 13.89 seconds; $t = 4.092$, $df = 6$, and $P < 0.01$.

The maximum systolic blood pressure during the seizure was invariably either higher or the same when Metrazol had been administered and the same tendency was observable as regards pulse fre-

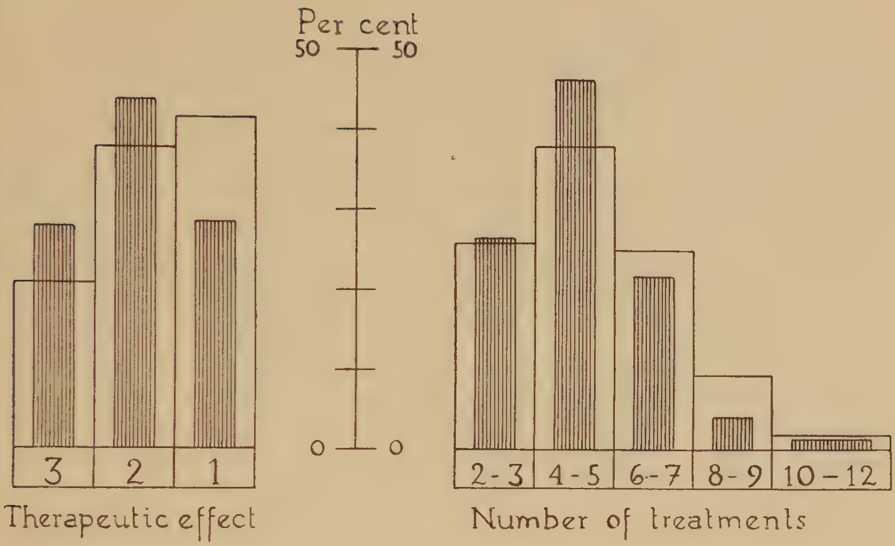

Fig. 1.
Percentage distribution of the therapeutic effect of treatments (expressed numerically, 1–3) and the number of treatments required, without muscular relaxation (blank columns) and with muscular relaxation (shaded columns).

quency. These differences were inconsiderable and were not statistically significant.

V. *The therapeutic effect of electric shock treatment in connection with routine muscular relaxation.*

The therapeutic effect of series of electric shock treatments in connection with routine muscular relaxation and administration of oxygen (151 cases in 1951–52) was compared with the effect of series of treatments without muscular relaxation (108 cases in 1949–50). Only cases designated by the head psychiatrist as endogenous depression were taken into account. The number of treatments that were required in each case and the therepeutic effects described in the case-sheets were compared. The effects are expressed numerically: 1 (slightly improved), 2 (distinctly improved) and 3 (recovered).

From *Fig. 1* it will be seen that the therapeutic effect tended to be better when muscular relaxation had been employed, in spite of the fact that not quite so many shock treatments had then been found necessary. When muscular relaxation was not employed the average therapeutic effect was 1.787 ± 0.07217, and 2.000 ± 0.06161 when it was applied. The difference was nearly significant; $t = 2.140$, $df = 257$ and $P = < 0.05$.

The number of shocks that had been considered necessary when muscular relaxation was not used was 4.981 ± 0.1907, and 4.642 ± 0.1408 when it was applied. The difference was not significant; $t = 1.430$, $df = 257$ and $P = > 0.05$.

On investigating the age distribution of the two groups it was found that the patients to whom unmodified electric shock treatment had been administered had an average age of 47.0 ± 1.22 years, while the average age of patients to whom muscular relaxation had been employed was 51.3 ± 0.95 years. The difference (4.3 years) was significant; $t = 2.788$, $df = 257$ and $P < 0.01$. It might then have been presumed that distribution of age had influenced the results, but on dividing the patients into various age groups: 20–39 years, 40–59 years and 60–79 years it was found that in all three age groups the effect tended to be better when muscular relaxation was employed.

The patients who received unmodified treatment consisted of 50 men and 58 women, while the group in which muscular relaxation had been employed comprised 81 men and 69 women. Thus the proportion of male patients was higher in the latter group. In this group, however, the therapeutic effect tended to be better for both men and women than it was for the group in which unmodified treatment was administered.

If the material was divided into two groups: fairly "pure" typical cases of depression and more atypical cases, there was still a tendency towards a better therapeutic effect in both groups when muscle relaxants and oxygen were administered. Furthermore, during the period 1949–52 no changes in the principles of administering electric shock treatment were introduced at the hospital which could have effected the results obtained.

DISCUSSION

The investigations made clearly show that the duration of the convulsions induced by electric shock treatment is the more prolonged the higher the degree of muscular relaxation and of oxygen saturation. When the musculature is relaxed, less oxygen is consumed. Moreover, when there is total muscular relaxation oxygen may readily be administered continuously so that a state of supersaturation may even be attained. Furthermore, the circulation is less impaired when the muscular convulsions are eliminated (*Holmberg & al.* 1954). The prolongation of the seizure was already highly significant when routine muscular relaxation and administration of oxygen were applied, and considerably further prolongation was observed when there was total muscular relaxation and insufflation of oxygen. Under these ideal physiological conditions it was found that the epileptic seizures could be prolonged up to 7–9 times their usual duration.

The fact that the duration of the convulsions could not be timed with a stop watch in the usual way when muscle relaxation was total, may be considered an imperfection. In that case the exact time of the cessation of the convulsions could not be accurately observed on the exterior of the patient, and consequently the duration of the convulsions had to be recorded electroencephalographically. However, on the basis of several experiments, we have convinced ourselves that during partial muscle relaxation the visible muscular twitchings and the EEG activity cease simultaneously, and hence the two methods of timing ought to be equivalent. Furthermore, the difference in the durations of the convulsions was in fact so great, that a possible slight methodical error could hardly be expected to affect the result.

The experiments with nor-adrenalin and amyl nitrite were carried out in order to ascertain the part played by the blood pressure as regards the seizure. During epileptic seizures the blood pressure invariably increases very considerably, even when the muscular convulsions are eliminated (*Holmberg & al.* 1954). This is probably due to the production of pressor-substances, and it is likely that these in turn favour the continuation of the seizure. As was pointed out by *Ruf* (1951), adrenalin has the effect of greatly stimulating the seizure. We did not wish to administer adrenalin, however, as this might give rise to an excessive direct excitation of the heart. We had observed an accumulation of ventricular extra systoles, even in electric shock treatment without the administration of chemical stimulants. The main effect of nor-adrenalin is to increase the blood pressure, and in contrast to adrenalin it decreases heart frequency, and for this reason it was decided to use it in our experiments. A certain tendency for the duration of the seizures to be prolonged was noticeable, but as this was not considerable, the experiments were soon discontinued. Nor-adrenalin, as distinguished from adrenalin, does not give rise to any increase in cerebral circulation, on the contrary, it is more liable to cause its decrease (*King & al.* 1952, *Sensenbach & al.* 1953), which explains why it has only a slight effect on the seizure. Our results, however, do not afford any grounds for assuming that cerebral metabolism is diminished by nor-adrenalin. Also *Minz & Domino* (1953) found that nor-adrenalin as well as adrenalin enhanced cerebral after-discharges. On the other hand, in view of our experiments and those made by *Reitman and Richards* (1945), which showed that amyl nitrite raised the convulsive threshold, it is probable that substances, such as nitrites, which dilate the blood vessels, decrease cerebral metabolism during a seizure. Cerebral circulation is probably diminished by the nitrites owing to the decrease in blood pressure which they cause.

Metrazol was shown to increase the duration of the seizure. At the same time the circulatory effects were apparently somewhat greater than usual. It is probable that the prolongation of the seizure was due to an increase in cerebral circulation and metabolism. It is also possible to assume that a continuous chemical stimulation of the nerve cells was the cause of the prolongation. Against the latter assumption it may be stated that the brain appears to be refractory to stimuli when a maximal epileptic discharge has begun (*Toman & al.* 1948). On the other hand, it has been shown that in animals epileptic seizures are influenced by a change in cerebral circulation (*Gellhorn* 1952). Consequently it is most likely that Metrazol is capable of stimulating an epileptic seizure because of its effect on the circulation. It is assumed that the effect of Metrazol on the circulation is due to its action on the central nervous system. Metrazol only exerts a definitive circulatory effect when quantities are administered which approach to the convulsive dose, which also agrees well with our results.

Since cerebral discharge during electric shock treatment is probably the requisite for the therapeutic effect taking place, it seems reasonable to suppose that a quantitative increase in the seizure should also augment its therapeutic effect. A number of cases where the seizure was prolonged to a moderate extent were investigated with a view to ascertaining the therapeutic effect. It was found that for cases of depression the increase in therapeutic effect was nearly significant, in spite of the fact that it had proved necessary to administer only a somewhat (not significantly) smaller number of treatments to each patient. This superiority to the unmodified treatments seems to be independent of the patient's sex or age or of the type of depression.

An investigation of this kind is bound to have a number of defects. Probably the most serious of these is that a comparison is made between two samples of different date and where there is an interval of 4 years between the first and the last observations made. Moreover, no definite norm exists for either the number of electric shock treatments that ought to be administered or for the way in which the effects of treatment should be judged. The patients were kept under observation only as long as they remained at the hospital. We do not believe that much more can be obtained from the present material, but it may perhaps be possible to demonstrate the validity of the theory advanced here, by selecting as far as possible definite cases of endogenous depression and by treating them under "ideal" conditions (total muscular relaxation and continuous administration of oxygen), and finally, by observing the number of treatments required definitely to cure the depression.

No investigation of this kind has as yet been undertaken. On the other hand, it has been observed that more treatments than usual are required if the seizures are reduced by pretreatment with anti-convulsants (*Holt & Borkowski* 1951). It has not infrequently been asserted that seizures induced by Metrazol have a better therapeutic effect than those induced by electric shock, while at the same time there appears to be a greater risk of fractures occurring in connection with Metrazol shocks. This appears plausible, since, according to our findings, Metrazol induces more intensive seizures than electric shock does. In spite of this it is hardly possible to recommend the resumption of Metrazol shock treatment, as circulatory and other risks may prove unnecessarily great in comparison with those connected with electric shock treatment (cf. *Toman & al.* 1948).

SUMMARY

By means of experiments in electric shock treatment the possibility of prolonging the epileptic seizure was investigated. In the main the following results were obtained.

1. When routine muscular relaxation together with inhalation of oxygen was applied, a very significant prolongation of the seizure occurred up to an average duration of over 70 seconds.

2. When there was total muscular relaxation and continuous insufflation of oxygen the seizure was further prolonged, and the average duration was 2–3 minutes. In individual cases the duration was even 4–6 minutes.

3. Infusion of l-nor-adrenalin did not appreciably increase the duration of the convulsions. Inhalation of amyl nitrite decreased the duration. It is assumed that these effects are due to the action of these substances on cerebral circulation.

4. Preconvulsive injection of Metrazol, when large doses were administered, gave rise to a significant prolongation of the duration of the convulsions, and when Metrazol itself induced a seizure its duration was especially long. The probable reason for this is a centrally effected circulatory stimulation.

5. The hypothesis that the therapeutic effect in cases of depression is related to the duration of the seizure, has been tested on groups of patients routinely treated with and without muscle relaxants and oxygen administration. The therapeutic effect, when the modified technique was applied, was found to be almost significantly greater than that of the unmodified treatment, in spite of the fact that a somewhat (not

significantly) smaller number of treatments were required when the modified technique was adopted. The therapeutic effect of electric shock treatment when there is total muscular relaxation and continuous administration of oxygen has not yet been determined. It seems probable that Metrazol shock treatment is capable of producing a greater therapeutic effect than that obtained by means of electric shock treatment, but the latter mehod is nevertheless to be preferred.

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CEREBRAL BLOOD FLOW IN ARTERIOVENOUS ANOMALIES OF THE BRAIN DETERMINED BY THE USE OF RADIOACTIVE KRYPTON 85

By

N. A. LASSEN and O. MUNCK

Since the introduction of the nitrous oxide method for quantitative determination of the cerebral blood flow (*Kety* and *Schmidt,* 1945) it has been possible to obtain knowledge of the physiological changes in cerebral circulation in patients with arteriovenous anomalies of the brain, and it is well established (*Shenkin, Spitz, Grant,* and *Kety,* 1948; *Bessman, Hayes, Alman,* and *Fazekas,* 1952; *Bernsmeier* and *Siemons,* 1952) that a marked increase in the cerebral blood flow and a decrease in the cerebral arteriovenous oxygen difference can be demonstrated. However, complete studies before and after radical surgery on patients of this category have hitherto only been published in one case (*Bessman, Hayes, Alman,* and *Fazekas,* 1952), where the original nitrous oxide technique was used. In the present paper two further cases are presented. The krypton 85 method (*Lassen* and *Munck,* 1955) was employed, using blood from both internal jugular veins as representative of cerebral venous blood.

METHOD

The cerebral hemodynamics were determined by means of radioactive krypton 85 (Kr^{85}) (*Lassen* and *Munck,* 1955). This method is based on the same principle as the nitrous oxide technique, viz. the exchange of an inert gas between blood and brain. Indwelling needles were placed in the superior bulbs of both internal jugular veins and in one femoral artery. The subjects inhaled atmospheric air containing radioactive Kr^{85} for 14 minutes during which period blood samples from the three vessels were drawn. Kr^{85} saturation curves were drawn for each vessel from the relative concentrations measured in the blood

TABLE 1

The cerebral metabolism and hemodynamics in two cases of abnormal arteriovenous intracranial shunting studied before and after removal of the shunt. In both cases the angioma was situated in the right hemisphere.

	Case 1		Case 2	
	before	after	before	after
Cerebral (A–V)O_2 (vol.%)				
Right	2.5	5.9	0.8	3.7
Left	5.6	5.9	4.0	5.5
Cerebral O_2 consumption (cc./100 g./min.)				
Right	4.4	2.5	1.8	3.4
Left	2.5	3.0	4.3	3.3
Mean arterial blood pressure (mm Hg)	89	90	110	121
Mean internal jug. blood press. (mm Hg)				
Right	8	4	14	9
Left	5	7	6	8
Cerebral vascular resistance (mm Hg/cc. blood/100 g./min.)				
Right	0.5	2.0	0.4	1.2
Left	1.9	1.6	1.0	1.9
Internal jugular oxygen saturation (%)				
Resting subject				
Right	82	58	87	69
Left	65	58	71	57
After inhal. of 7 % CO_2 for 2 min.				
Right	89	75	90	82
Left	80	75	82	72
Arterial carbon dioxide tension (mm Hg)	33	—	36	42
Hemoglobin concentration (g./100 cc).	13.2	12.4	14.6	11.2
Dementia	+	+	—	—
Cerebral blood flow (cc./100 g./min.)				
Right	176	43	222	92
Left	45	51	108	59
Average (p. 73)	92	47	155	74
Estimated "normal" value (p. 73)	45	45	50	60
Volume of blood passing shunt (cc./min.)	600	0	1500	200

samples, and the cerebral blood flow (CBF) in cc./100 g. brain/min. was calculated separately for each internal jugular vein according to the equations published elsewhere (*Lassen* and *Munck*, 1955). However, no correction was necessary for the arteriovenous delay in cases of abnormally high flow, as the time lag between the beginning of the arterial and venous curves was absent in these cases (figures 5 and 6).

The blood flow of the shunt.

An estimation of the blood flow of the shunt can only be made if the weight of the brain and the pattern of the venous outflow from the brain are known as well as the CBF the subject could be expected to have had if no shunt had been present. These factors can only be roughly estimated. Furthermore, the accuracy of the individual CBF values decreases with increasing CBF. The calculated blood flow of the shunt can therefore only be considered to be a gross approximation.

The blood flow of the shunt was calculated from

$$\text{SHUNT} = 14\ (\text{CBF}^{\text{A}} - \text{CBF}^{\text{E}})\ \text{cc./min.}$$

on assuming the weight of the brain to be 1400 g. CBF^{A} is the average CBF of the values obtained from the two sides. In order to calculate this average two patterns of the venous outflow from the brain were considered: The two superior bulbs were assumed (1) to drain equal volumes of blood or (2) to drain areas of the brain of equal weight. As the mean jugular blood pressure was higher on the side with the higher CBF (Table 1) assumption (1) was found unlikely. However, the higher pressure on the side with the higher CBF could be expected to direct venous blood to the contralateral intracranial venous channels, and assumption (2) would also be erroneous. To avoid these extremes the average CBF ($= \text{CBF}^{\text{A}}$) was calculated as the arithmetical mean value between the values calculated by using assumption (1) and (2), i.e.:

$$\begin{aligned}\text{CBF}^{\text{A}} = {}& {}^1/_2\,[2\ \text{CBF}^{\text{right}}\ \text{CBF}^{\text{left}} / (\text{CBF}^{\text{right}} + \text{CBF}^{\text{left}})] \\ &+ {}^1/_2\,[{}^1/_2\ \text{CBF}^{\text{right}} + {}^1/_2\ \text{CBF}^{\text{left}}]\ \text{cc./100 g./min.}\end{aligned}$$

CBF^{E} is the average CBF the subject could be expected to have had, if no shunt had been present. The CBF^{E} was estimated from the normal value of 52 cc./100 g./min. previously reported by the authors (Lassen and Munck 1955), taking into account the hemoglobin contents of the blood, the arterial carbon dioxide tension, and the mental state of the patient (i.e. signs of dementia).

CASE REPORTS

Case 1. N.H.J., a 42-year-old fisherman. He was born in 1912, had from 1938 to 1946 several generalized epileptic seizures. In 1946 a right side premotor angioma was found angiographically (Figs. 1 and 2), and a partial ligation of the right internal carotid artery was performed. After an interval of one year, the attacks recurred as left-sided Jacksonian motor seizures at intervals of one to two months. Phenobarbital did not control the convulsions. In July 1954 the patient was admitted to the neurosurgical ward at the University Hospital of Copenhagen. Examination disclosed a morose and intellectually reduced patient. The plantar responses were

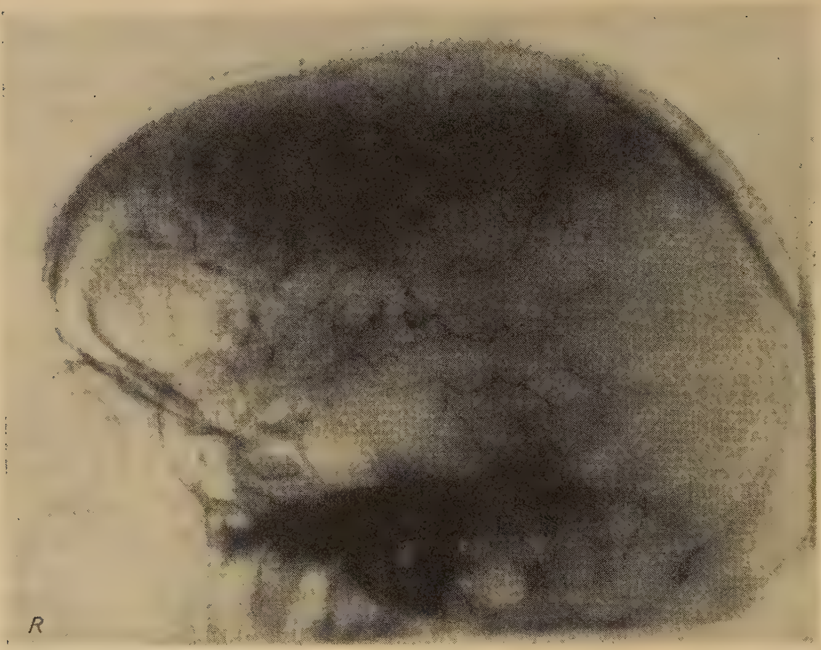

Fig. 1.
Case 1. Arteriogram, right side.

extensor. Lumbar encephalography showed diffuse enlargement of the lateral ventricles most pronounced on the right side. Carotid arteriography was made on both sides and the right-sided angioma was again found, but no other signs of abnormal vessels were seen. The patient had no cardiac complaints, and cardiological examination was not carried out. At the operation on August 3, 1954, an angioma racemosum with arteriovenous shunting was excised from the right frontal lobe, in which a wedge-shaped resection reaching the falx was made. Histological examination showed typical angioma racemosum cerebri. Postoperative bone necrosis retarded reconvalescence, and a postoperative incomplete left-sided hemiparesis receded gradually. The signs of dementia were somewhat more pronounced than before operation, but no epileptic seizures have occurred in the 7 months after the operation in which the patient has been observed. The postoperative study of the cerebral circulation was performed two months after the operation.

Case 2. E.F.L., a 43-year-old carpenter, had noticed slight impairment of vision for some months when in July 1954 he had an epileptic seizure of more than one hour's duration. Three weeks later he had another attack, lasting only one minute. In August 1954 he was admitted to the neurosurgical ward at the University Hospital of Copenhagen. Examination showed nothing abnormal, especially it was noted that the field of vision was normal and the intellectual capacity unaffected. Lumbar encephalography was normal. Carotid angiography was performed on both sides, and in the right occipital region an abnormal vascular configuration was found (Figs. 3 and 4). No other vascular anomalies were disclosed. Angiography of one

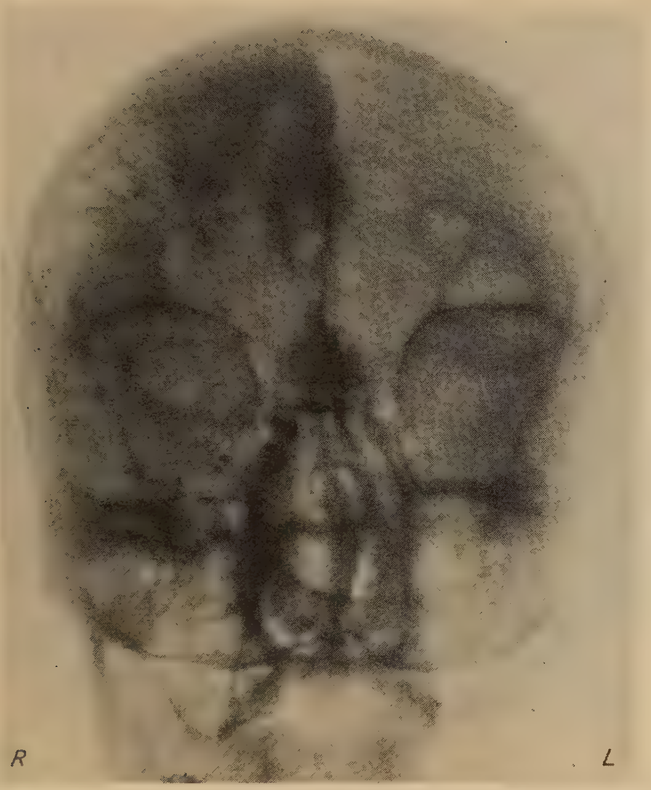

Fig. 2.
Case 1. Arteriogram, right side.

of the vertebral arteries (the right) showed normal conditions. The patient had no cardiac complaints. ECG and chest X-ray were normal. At the operation on August 25, 1954, the pole of the right occipital lobe was resected. Multiple arteriovenous shunts with tortuous and hypertrophied vessels were clipped and removed. Several abnormal vessels connected the angiomatous structures and the confluence of the sinuses. Histological examination showed a typical angioma racemosum cerebri. The postoperative course was uneventful. A left-sided homonymous hemianopsia was noted. Postoperative right-sided carotid angiography failed to show any abnormal vessels. The intellectual capacity was uninfluenced by the operation. The postoperative study of the cerebral circulation was performed two weeks after the operation.

RESULTS

The results of cerebral circulatory studies before and after operative removal of an abnormal intracranial arteriovenous shunt are presented in Table 1, and in figures 5 and 6. The mean CBF before operation was abnormally high in both cases, 92 cc./100 g./min. in Case 1 and

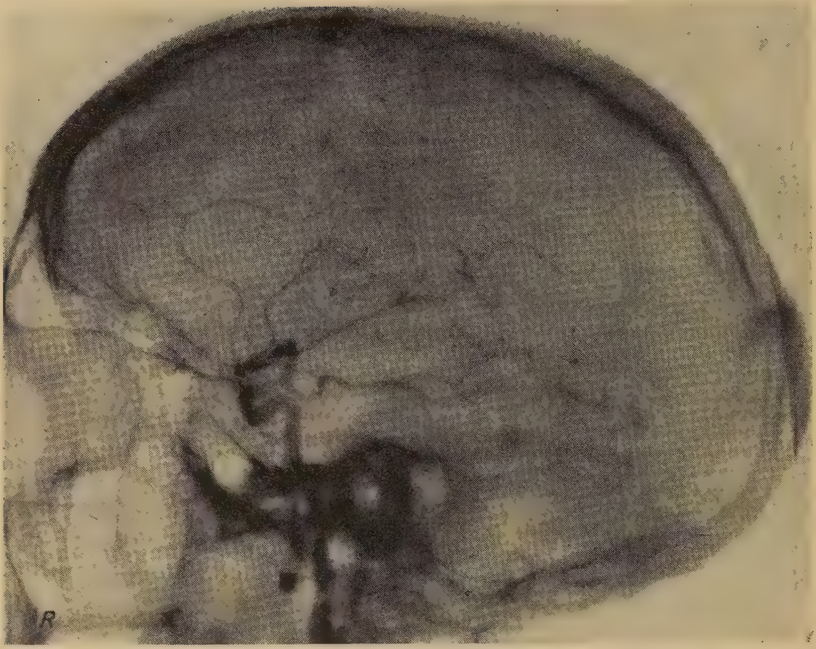

Fig. 3.
Case 2. Arteriogram, right side.

155 cc./100 g./min. in Case 2, as against 52 cc./100 g./min. in normal subjects (*Lassen* and *Munck*, 1955). After the operation the CBF was normal in Case 1 (47 cc./100 g./min.) and only slightly above normal in Case 2 (74 cc./100 g./min.). The approximate values for the blood flow of the shunts are seen in Table 1.

In all 4 bilateral determinations significant differences of CBF and $CMRO_2$ of the two sides were found (*Munck* and *Lassen*, 1955). The preoperative study in Case 1 is of particular interest, as abnormal shunting was only demonstrable in the right internal jugular vein. The angioma in Case 1 was situated in the right premotor region, and the close relation to the superior sagittal sinus strongly suggests that a considerable part of the angioma was drained via that vessel. If this is true, then no confluence of the sinuses can have been present in this case.

The moderately increased CBF of 74 cc./100 g./min. found postoperatively in Case 2 is suggestive of the presence of a minor remnant of the shunt. The anomaly was localized deep in the substance of the hemisphere, and complete operative removal was consequently difficult to ensure. Our figures indicate that nearly 90 % of the shunt had been removed. The postoperative right-sided carotid angiography in Case 2

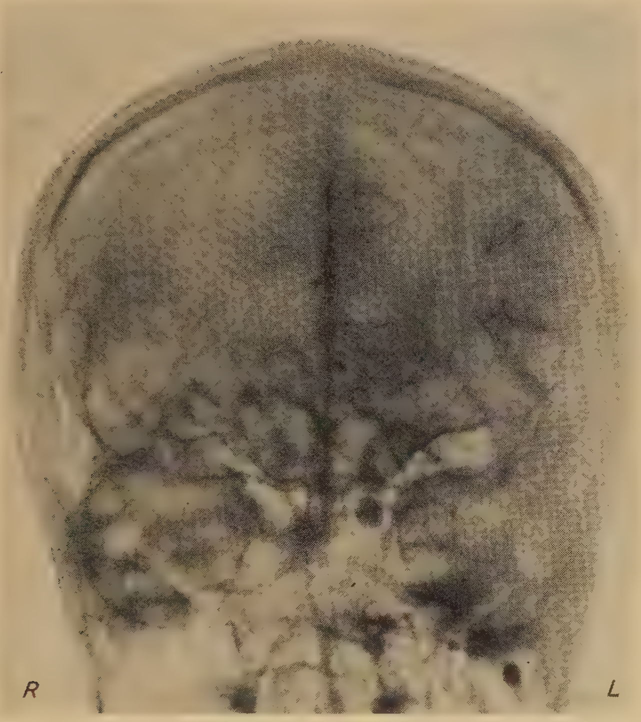

Fig. 4.
Case 2. Arteriogram, left side.

did not show any abnormal vessels, but this does not exclude a shunt, which owing to rapid blood flow may escape notice. The signs of shunting in the postoperative study in Case 2 were:

(1) Higher CBF (92 cc./100 g./min.) than so far observed by this method in normal subjects. This high flow on the right side was found simultaneously with a left CBF of 59 cc./100 g./min., which is somewhat higher than the normal average value of 52 cc./100 g./min. Thus in spite of the increased arterial carbon dioxide tension and the slight anemia, these results are suggestive of abnormal shunting.

(2) The high oxygen saturation of 69 % of the right internal jugular blood was increased to the very high value of 82 % after 2 minutes' inhalation of 7 % CO_2, 21 % O_2, 72 % N_2. These values are suggestive of abnormal shunting when compared to normal values (to be published).

(3) By retrograde extrapolation of the venous saturation curves (fig. 6) it was found that the right-side curve started almost simultaneously with the arterial curve, whereas the left-side curve started with the normal delay of approximately 15 seconds.

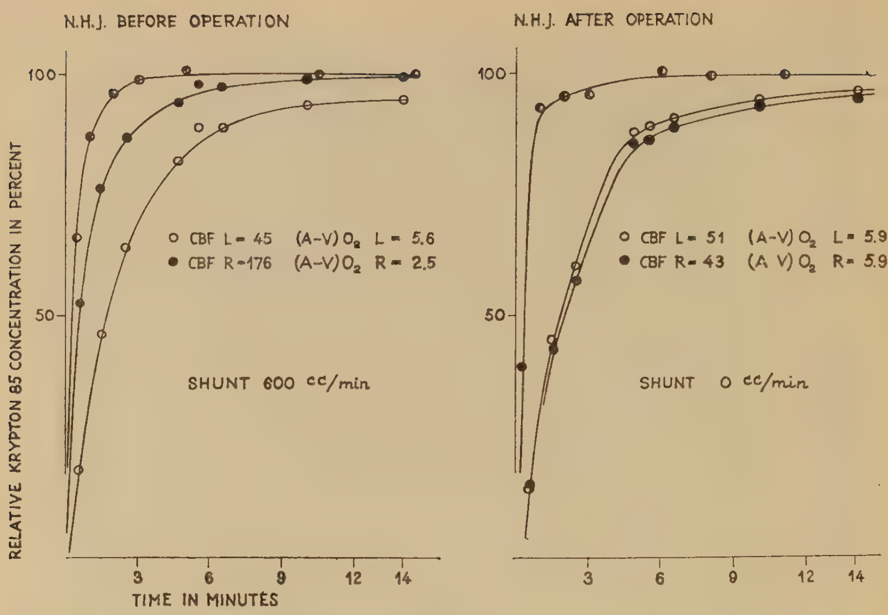

Fig. 5.

Case 1. Pre- and postoperative saturation curves for Kr^{85} in the femoral artery (◐ ◐ ◐) and in the superior bulbs of the two internal jugular veins (● ● ● right side, ○—○—○ left side). The CBF in cc./100 g./min., the cerebral (A–V)O_2 in vol.%, and the volume of blood passing the shunt in cc./min. are indicated.

DISCUSSION

Flow studies of vascular anomalies are of interest as a check on the validity of the method used. The results reported here support the accuracy of the krypton 85 method. It is of especial interest that the cerebral oxygen consumption was within the limits that could be expected from the clinical data, i.e. slightly below normal in Case 1 and normal in Case 2.

The inert gas diffusion techniques can demonstrate and approximately quantify a functioning intracranial shunt. Studies similar to those reported by us have been made with the nitrous oxide technique (*Shenkin, Spitz, Grant,* and *Kety, 1948; Bessman, Hayes, Alman,* and *Fazekas,* 1952; and *Bernsmeier* and *Siemons,* 1952), but complete pre- and postoperative bilateral studies after radial removal of the shunt have only been reported previously in one case (*Bessman, Hayes, Alman,* and *Fazekas,* 1952, Case 2). In the previous publications the basis for the quantitative evaluation of the flow of the shunt and the approximate limitation of the method have not been discussed. We have here tried to evaluate some of the factors of importance for the

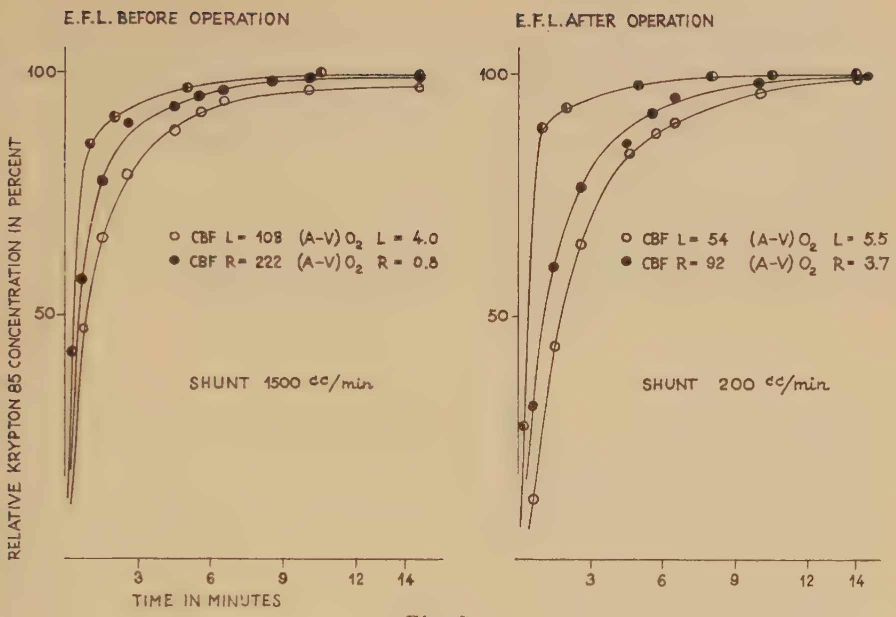

Fig. 6.

Case 2. Pre- and postoperative studies of the cerebral circulation. Signatures as in fig. 5.

calculation of the shunt flow. From the results of the postoperative study of Case 2, it was found that shunt values of 200 cc./min. represent approximately the smallest lesions demonstrable by the krypton 85 method.

By arteriography the larger vessels of the brain can be visualised, and often structures can be seen which, on the basis of structure and more or less rapid passage of the contrast medium, suggest a shunt. In this connection it is of interest that the arteriographically largest angioma (Case 1) carried less than half the volume of blood per minute of the less distinct angioma in Case 2. Quantitative considerations as to circulatory significance obviously cannot be made by arteriography alone. The semiquantitative evaluation of the shunt by the inert gas diffusion technique enables a consideration of the impact of the shunt on the general circulation, but the faculty of the organism to endure this stress is influenced by more factors than the mere size of the shunt. Neither of our two cases had any cardiopulmonary complaints.

SUMMARY

1. Bilateral studies of the cerebral blood flow by the krypton 85 method were carried out pre- and postoperatively in two cases of intracranial arteriovenous anomaly.

2. The preoperative values were considerably above the normal values, with preponderance on the side of the angioma. The mixing of cerebral venous blood was incomplete in all four studies. The postoperative values were normal in Case 1 and slightly abnormal in Case 2.

3. Besides being an aid in the clinical diagnosis of cerebral arteriovenous shunts, cerebral blood flow determinations may be useful as a control of the results of surgery.

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TRANSITORY VISUAL DISTURBANCES AFTER VENTRICULOGRAPHY

By

HANS MICHAEL LOSSIUS

Since *W. E. Dandy* in 1918 (1) introduced ventriculography as a diagnostic aid in intracranial disease, this method has obtained an important position in clinical medicine.

Ventriculography has been used for many years at the Neurosurgical Department of Rikshospitalet, Oslo, as a routine diagnostic procedure *per se,* i.e. without being followed immediately by a major operation. The patient has afterwards been left in peace until the effect of the ventriculography has passed over.

This has made it possible to observe some transitory disturbances of the optic system following the ventriculography. These disturbances are not of frequent occurrence, the incidence being only 3 cases out of 600 ventriculographies. Complications of this type apparently have not been described before, and the case histories will, therefore, be summarized below.

To begin with, a few words on the technique, which has always been the same and mainly the same as that of *Percival Bailey* (2).

Through symmetrical trephine openings in the posterior part of both parietal regions both lateral ventricles have been punctured by means of a rather thick, blunt needle with perforated sides, the needle pointing in a frontal-basal-median direction. Provided that the case has not been one of hydrocephalus, the amount of air insufflated has varied between 10 and 50 millilitres, the equivalent amount of cerebrospinal fluid being evacuated. The puncture has been performed as carefully as possible, and has been abandoned altogether after 3–4 unsuccessful attempts.

These are the cases we have observed:

Case 1: Woman aged 24. Six months prior to admission she suddenly experienced a pressing headache in both temporal regions, combined with nausea, vomiting and vertigo. During the next couple of months she had three similar attacks, all lasting approximately 12 hours. Two months before admission she had yet another attack, this time accompanied by red and green colour scotomata.

Examination upon admission revealed bilateral papilloedema (approx. 2 diopters). Vision and visual fields were completely normal, and the neurological examination revealed nothing abnormal.

Because the papilloedema was found to increase, ventriculography was performed after a fortnight, according to the technique described. There were no difficulties in connection with the procedure, and approximately 10 millilitres of air were insufflated.

Directly afterwards a striking bilateral exophthalmus was noticed, and the patient herself felt as if the bulbi were being pressed forward. At the same time she became *totally amaurotic.*

That evening she could distinguish between light and dark, and further improvement of vision had taken place next day. The exophthalmus remained on both sides in a somewhat varying degree for the next two days, and by Donders' method a slight, left-sided homonymous hemianopsia could be demonstrated.

Vision improved slowly during the next few days, progress being slower on the left than on the right side.

13 days after the ventriculography she was examined in the Ophthalmological Department, and a definite diagnosis of left-sided, homonymous, lower quadrant anopsia was made. Papilloedema had increased, but vision on both sides was normal. Examination 2 months after the ventriculography gave the same result, but one month later nothing abnormal was detected as regards vision, fields of vision and optic papillae. Neither did the neurological examination reveal anything abnormal.

The ventriculography showed slight asymmetry of the lateral ventricles, and the final diagnosis was: Increased intracranial tension of unknown cause.

Case 2: Woman, aged 36. 18 months prior to admission she had a nocturnal epileptic fit of the grand mal type. One month before being admitted she had another fit. No visual disturbances.

Examination upon admission revealed:

(1) Bilateral papilloedema of approx. 2 diopters. Vision 5/10 on both eyes. Field of vision normal, estimated by Donders' method.
(2) Doubtful, alternating paresis of the facial nerve of the central type.
(3) Slight preponderance of deep reflexes on the left side, Babinski type of plantar response on the left side, and weakened abdominal reflexes on the left side.
(4) Slight tremor of right arm.

Ventriculography was performed by the usual method. The needle entered the left ventricle easily, but the puncture was unsuccessful on the right side, the operator had furthermore the impression that the needle passed through abnormal tissue on the right side. Approximately 25 millilitres of air was insufflated into the left ventricle.

Shortly afterwards the patient complained of blurred vision. She could dimly see the clock in the theatre, but could not tell the time. A couple of hours later, however, she could read her own small wrist watch. She was examined the day after in the Ophthalmological Department, and neither vision nor papilloedema were found to have changed. The appearance of the retina, however, was described as oedematous, and a marked diminution of the visual field affecting the nasal quadrant of the right eye was observed. The field of vision of the left eye was normal.

Ophthalmological control examination repeated on the 4th, 7th and 16th day after the ventriculography revealed a left-sided, homonymous lower quadrant anopsia, to begin with for red, later also for white.

Clinical examination as well as ventriculography, carotid angiography and electroencephalography pointed to the presence of a tumor in the right parieto-occipital region. 17 days after the ventriculography craniotomy was performed, and a meningioma was removed from that region. A complete, left-sided, homonymous hemianopsia persisted after the operation.

Case 3: Woman, aged 22. Her symptoms began in 1945, at the age of 15. Periodically she had pain in the left temporal region, later on the left side of the nape of the neck and back part of the head. In connection with the attacks of headache she began, in 1949, to see black spots in the temporal visual field of the left eye, and from 1953 she also experienced an oppressive sensation behind the left eye. Furthermore she had gyratory vertigo, numbness of the left side of the face and tinnitus in the left ear.

When she was admitted in 1954, she presented the following signs:

(1) Bilateral papilloedema, 1–2 diopters. Vision normal, field of vision normal ascertained by Donders' method.
(2) Slight exophthalmus and ptosis on the left side.
(3) Weakened corneal response on the left side and hypesthesia corresponding to the first and second branch of the left trigeminal nerve.
(4) Preponderance of deep reflexes on the left side, weakened abdominal reflexes on the same side and Babinski type of plantar response on the left side.

5 days after admission diagnostic ventriculography was performed, as electroencephalography and carotid angiography had both failed to reveal any definite pathological signs. Puncture of the left lateral ventricle was easily performed, but on the right side the procedure had to be given up. 20 millilitres of air was insufflated on the left side.

When this was carried out, the patient complained of seeing red and blue scotomata moving about in the left half of the visual field. They merged into one bright, cloudy scotoma covering the whole visual field so that she was unable to see her own hand when she held it up in front of her. She could, however, distinguish between light and dark. Her condition was otherwise good.

Her sight improved somewhat already the same day, and two days later she could see better than 5/10 bilaterally. That same day a left-sided, homonymous, lower quadrant anopsia could be demonstrated. Ophthalmoscopy revealed contracted vessels, particularly arteries.

A control examination 3 days later showed the same defects in the field of vision, but to a lesser extent, and the next day no defects of the visual fields could be demonstrated by Donders' method. Perimetric examination after 11 days showed that the border lines of the visual fields had become normal, although the patient had a subjective sensation of some blurring of vision in the temporal visual field of the left eye. Vision was 5/5 bilaterally.

The ventriculography revealed possible changes in the region of the anterior horn of the left ventricle. Diagnosis: Increased intracranial tension of unknown cause.

In these 3 cases transitory complications in connection with the ventriculography were observed. They consisted in reduction of vision down to complete amaurosis, as well as defects in the visual fields, in all cases registered as a left-sided, homonymous, lower quadrant anopsia.

The diminution of vision in all cases lasted only a few days, whilst the reduction in the visual fields was demonstrable over a long period, in Case 1 more than 2 months, in Case 3 approximately one week, whilst the duration in Case 2 cannot be estimated, as craniotomy 17 days after the ventriculography resulted in a persistent homonymous hemianopsia.

In two cases (1 and 3) no intracranial disease was detected, whilst one (Case 2) had a meningioma.

DISCUSSION

It is unlikely that the complications described resulted from a direct trauma upon tissue conducting visual stimuli. Using the technique mentioned, the only possibility could be lesion of the optic radiation, the path of which runs in front of and lateral to the posterior part of the ventricles before heading for the occipital lobe. By inserting the needle from the posterior parietal region in a frontal-basal-median direction practically no risk is run of damaging the optic radiation. Furthermore, traumatic lesion of the optic radiation would hardly result in *temporary* complications, and a diminution of vision to the extent of amaurosis, which has been recorded, would require extensive damage of the optic radiation on *both* sides. This is most improbable, practically beyond possibility. And a direct trauma most certainly would not explain the reduction of the visual fields, which later on could be demonstrated and, together with the information about colour scotomata (Case 3)—points to a cortical affection around the calcarine fissure, i.e. in the region of the occipital pole. That this region should suffer any direct damage during ventriculography, is out of the question.

When performing ventriculography on Case 2, the operator thought that the needle passed through abnormal tissue on the right side. This patient was later operated for a meningioma on the same side, and it is possible that the puncture needle may have caused a haemorrhage inside the tumor. This, however, does not tally with the fact that the diminution of vision did not last for more than a couple of hours, nor did the removed specimen show any sign of such haemorrhage.

The most probable explanation of the recorded visual phenomena is a derangement of the cerebral vasomotoric control caused by the ventriculography. It is well-known from general surgery that the response of an artery subjected to trauma is contraction, later followed by a dilatation—a reaction commonly observed in the days when arterial neurectomy was used.

In accordance with this one must assume that the traumatism of cerebral vessels, which ventriculography entails, sets up a circumscribed or general vasocontraction by means of a reflex mechanism. This vasocontraction in turn causes ischaemia, which again results in hypoxia or anoxia. The process is usually a reversible one, and thus explains the transitory nature of the visual disturbances.

The fact that the area of the calcarine fissure should be particularly vulnerable in this respect—as our three cases seem to indicate—, may be due to several factors.

This area is of very limited extent and has a most delicate function. Consequently one must presume that it is very sensitive to any disturbance in blood supply, and/or that the response to disturbances of this nature results in easily demonstrable symptoms and signs.

From other pathological conditions caused by insufficiency of arterial blood supply, we know that the distal parts of the area receiving this supply are first and most severely affected, as for instance in the case of angiosclerosis of the limb vessels. In the same way the occipital pole can—as regards blood supply—be said to belong to a peripheral part of the brain, being supplied merely by the finest, terminal branches of the posterior cerebral artery. One must presume that contraction of these narrow arteries will have a greater damaging effect on the area which they supply, than would be the case when more centrally situated vessels of wider diameter are affected.

The insufflation of air itself also acts as a trauma, causing disturbances of the vasomotor control of the cerebral vessels, as has been demonstrated by *I. W. D. Bull,* who in Modern Trends in Neurology 1951 reports that postmortem examinations after ventriculography show that the brain is hyperaemic and slightly swollen (3).

Some of the other findings in our three cases also support the assumption that the visual disorders are caused by vasomotor disturbances: in Case 1 transitory alternating exophthalmus was noticed, in Case 2 oedema of the retina, which also was transitory, and in Case 3 concurrent contraction of the vessels in the fundus oculi could be demonstrated distinctly.

It is striking that all three cases presented the same defects in the visual fields, namely a left-sided, homonymous lower quadrant anopsia, indicating that the right striate area was affected. This may, of course, only have been a coincidence as there are too few cases to allow any conclusions to be drawn from this fact.

SUMMARY

Some rare complications after ventriculography have been observed at the Neurosurgical Department of Rikshospitalet, Oslo. Three cases are reported who in direct connection with the ventriculography developed visual disturbances consisting of various degrees of diminution of vision, even amaurosis, and in defects of the visual fields, in all three cases consisting of a homonymous defect in the lower, left quadrants. All complications were transitory.

After a short discussion the author arrives at the conclusion that the disturbances result from derangement of the vasomotor control of cerebral vessels, caused by the surgical intervention of ventriculography.

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THE CLINICAL ASPECT OF CEREBRAL ANOXIA[2]

By

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States of anoxia have occurred as long as clinical medicine have existed or even before, although the name *anoxia,* introduced by *Peters* and *van Slyke* in 1931, has not been in frequent use till the last 5 or 10 years.

Formerly, e.g. in my undergraduate days, the term *asphyxia,* which literally means 'pulselessness', was used for all kinds of anoxic states, often, but by no means always, complicated by hypercapnia. Although some very conservative people occasionally still use this misnomer, it should in my opinion now disappear from our nomenclature as a term signifying anoxia.

We should now use the following terms:

Anoxia for complete or next to complete lack of oxygen in the air, in the blood or in the tissues,—and *hypo-oxia* for a partial lack of oxygen in air, blood, or tissues.

The term *anoxemia* resp. *hypoxemia* was introduced by *Barcroft* already in 1914 for complete or incomplete lack of oxygen *in the blood* and should only be used in this limited sense.

For the understanding of the clinical picture and the development of the various anoxic states it is of fundamental importance always to bear in mind *the enormous difference in tolerance to anoxia which obtains between the different body cells.*

In the first place nerve cells are more vulnerable than most of the other cells of the body. Then there is also a very great difference in this respect between the different levels of cells within the central nervous system. On the basis of the experimental work of *Heymanns* and others we assume that *cortical cells cannot survive anoxia of more than 5 to 10 minutes' duration, that the cells in the basal ganglia likewise perish*

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[1] Series 2, no 218.

[2] Paper read in abridged form at the Scandinavian Neurological Congress in Lund, June 1955.

after 5 to 10 minutes (*average 8 minutes*), that *cerebellar cells can survive up to 13 minutes' anoxia,* those of the medulla oblongata (respiratory and cardiovascular centres) 20 to 30 minutes and cells of the spinal cord 35 to 60 minutes. If anoxia exceeds these time limits, the disturbances resulting from the anoxic damage will be permanent. The anoxia has then not only "stopped the machine but wrecked the machinery", to use *Haldane's* expression.

The above-mentioned average values, which represent the time limit of the reversible processes in the damaged cells, are by no means absolute, but subject to the influence of several factors. It is obvious that the oxygen demand has a deciding influence, every bodily function increasing the demand and thereby the deficit of oxygene, thus accelerating the effects of an arrest of oxygen supply. Rise of temperature will increase the vulnerability of the cells, lowering of the body temperature on the other hand increase their tolerance to anoxia. Already *Paul Bert* in 1875 showed that there is a great difference between quite young and newborn individuals with greater tolerance, and older individuals with comparatively much greater vulnerability to anoxia. Apparently already *Robert Boyle* (1659) was awere of this and it has been verified by subsequent experimental and clinical studies.

In the clinic further elements of uncertainty generally complicate the picture. In the first place we seldom know exactly *when* anoxia has started, nor how long it has lasted, being not as a rule called in until the anoxic disturbances are already well established. Thus we are rarely in a position to tell whether the time limit for reversible processes has been overstepped or not. At least not at the beginning; it is as a rule the subsequent course of events that solves this question, the permanent disturbances corresponding to the extent of irreversible damage, the transient disturbances corresponding to reversible pathological changes.

Furthermore in the clinic the majority of cases have rarely been subjected to the complete—or nearly complete—anoxia of experimental work, but all degrees of hypo-oxia. Now, the less pronounced the hypo-oxia is, the longer time it will take to cause damage, and the easier other factors such as hypercapnia (CO_2 values exceeding 10 % cause loss of consciousness), hypocapnia (reduction of CO_2 means loss of a normal respiratory and circulatory stimulus), hypoglycemia, the influence of certain drugs, etc., may come into play and confuse the clinical picture. There is here a scale with a wide range. In this report I shall first and foremost deal with such conditions under which anoxia or a severe hypo-oxia constitutes the principal—if not the only—pathogenetic factor. This "*major anoxia*" sets in very quickly, is therefore an *acute anoxia,* but can have its chronic sequelae, if the patient survives the acute stage.

From the above-mentioned fact that the nerve cells are much more vulnerable to anoxia than most other body cells we understand that any condition of generalised anoxia will chiefly present a neurological clinical picture. And furthermore, as the cells of the cerebral cortex and the basal ganglia (chiefly the pallidal cells) are much more vulnerable than other nerve cells (the central nervous system withering from the top downwards), we easily understand that a general anoxia will first and foremost present a corresponding cerebral picture[1].

Let me further remind of the fact that the various regions and laminae of the cortex and the basal ganglia may be unequally affected (varying "Pathoklise" of the *Vogts*) and that the anoxic lesion more often consists in a focal or "spotty" necrosis of cerebral cells, as strongly emphasised by *Courville*[2].

This explains that in the different clinical types and individual cases variations occur. Allowing for such variations it should, however, be emphasized that there is a "striking similarity of the symptoms regardless of the method by which anoxia is produced," to quote *Steegman*. We may with this author divide the chief symptoms of anoxia ("major anoxia") into the following five main groups:

1. Disturbance of consciousness.
2. Psychic changes.
3. Visual and sensory defects.
4. Motor symptoms which are cortical, extrapyramidal, and decerebrate.
5. Changes in respiratory and autonomic functions.

All these symptoms may be transitory or permanent, dependent on the underlying cellular changes having passed the limits of reversible stages or not (cf. above). They may possibly be recurrent or progressive, owing to the possibility of the anoxic lesion taking on a progressive course. (Proliferation of endothelium, obstructing blood vessels and glia proliferation).

1. *Unconsciousness* is generally profound in all types of oxygen deprivation. It is often prolonged for a number of hours and may never

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[1] In this connection it is of interest to recall the fact that the brain, the weight of which amounts to only about 2 % of the total body weight, receives 20 to 25 % of the quantity of blood leaving the left cardiac ventricle.

[2] *Courville* seems to hold accompanying vascular changes responsible for this. I should like to suggest the possibility that normal differences of vascularity between the various areas might be partly (or wholly) responsible for this focal distribution of the necrosis, by some authors called "the hall mark" of anoxic necrosis.

return. In a case under my observation unconsciousness lasted until the patient died nearly five years later, after having existed as a living human decerebrate specimen all these years.

2. Of the *psychic changes* a transitory state of confusion, following the period of unconsciousness is the commonest. Emotional lability, euphoria, submaniacal states, more rarely depressive states, and all grades of intellectual loss down to the deepest dementia may also occur. Laughing, crying, and screaming, continuous talking and singing for hours have been observed, as on the other hand negativism and stubbornness, chiefly in the acute initial stage. "Peculiar emotional changes may materialize and so closely resemble hysteria that an erroneous diagnosis is frequently made." (*Steegman*).

3. Of *sensory disturbances, vision* in particular is affected in practically all cases of severe anoxia. Blindness may even be complete and is probably the result of peripheral as well as central damage. Impairment of hearing is also quite common. The impairment of vision and hearing are both quickly, but yet so gradually established that in mild cases the sufferer does not become aware of their existence until on an adequate oxygen supply he again regains his normal acuity of vision and hearing. This lack of insight has particularly been noticed in aviation, but is probably not confined to aviation anoxia.

As regards *other sensory functions*, paraesthesiae such as "pins and needles" are fairly common, but actual pains are extremely rare except for the headache that often follows (but rarely accompanies) anoxia. (That in aviation even severe *pain* sometimes may occur on rapid ascent to high altitudes, is *not* the result of anoxia, but of decompression as seen in divers' disease, depending on liberation of nitrogen within the body).

4. Of *motor disturbances* irritation phenomena, both tonic and clonic *convulsions* quite commonly appear at the initial stage,—and at later stages as well, if an epileptogenic focus has been established by a gliotic scar.

The *motor deficiency phenomena* are of no less importance. They consist in central paralyses of a *pyramidal* type or *extrapyramidal* syndromes of various distribution and intensity. States of decerebrate rigidity have also been observed. *Disturbances of coordination* may occur, too. In his very interesting book on Aviation Medicine (1952) *Armstrong* has a very instructive illustration showing ataxic handwriting at different degrees of altitude hypo-oxia.

5. Of *changes in respiration and autonomic functions Steegman* mentions respiratory failure and cardiac arrest, which when occurring

during general anaesthesia for obvious reasons may be the first symptoms to rouse attention. Cheyne-Stokes respiration is regarded as a warning sign of impending respiratory failure. The temperature may be raised and this may then become a link in a vicious circle as a rise in temperature tends to increase the vulnerability of the cells to anoxia, as already mentioned.

In order to obtain a useful and practical survey of the concrete clinical states of anoxia it is to my mind best to group them according to their different pathogenesis, and in this respect we may class the anoxias in the following groups:

1. *Anoxic or anaëric anoxia* caused by lack of oxygen in *the surrounding air*. Many authors use the term "anoxic anoxia" in a more comprehensive sense, extending this term to cover lack of oxygen in the airways right down to and in the alveoli. For practical reasons I think it better to use the term anaëric (suggested to me by my friend Krabbe to replace the inelegant, tautological expression anoxic anoxia) and to limit it to those cases where oxygen deficiency in the surrounding air is the causative agent and as a second group to list—

2. *Obstruction anoxia,* for that group of cases in which some obstruction in the airways, including the alveoli prevents the air from reaching the respiratory surface in the alveoli, where the oxygen passes from the air to the blood, there to unite with the hemoglobin of the erythrocytes and to be transported as oxyhemoglobin with the blood stream to the tissues.

3. *Paralytic anoxia,* caused by paralysis or incoordination of the muscular respiratory apparatus.

4. *Anæmic anoxia,* due to lack of sufficient hæmoglobin, necessary for the oxygen transport from the lungs to the brain and other organs.

5. *Stagnant anoxia,* the circulation of the blood being either stopped or slowed down to a rate insufficient for an adequate oxygen exchange.

6. *Histo-toxic anoxia* in which the tissue cells (the brain cells) have lost their power to absorb and utilize the oxygen, which the circulating blood brings at a sufficient rate and in sufficient quantity. In contradistinction to the previous groups, this kind of anoxia has no anoxemia as a link in the pathogenesis.

   Finally, in a large group of cases the above-mentioned different forms of pathogenesis are so mixed that it may be difficult to tell which is the principal one. This we may term

7. *Mixed or combined anoxia.* Under this group we may list that kind of anoxia which we have all run the risk of being exposed to during that critical natal episode of transition from placentar to pulmonary respiration.

We shall now deal separately with these various groups in turn and order, chosing some exemples of each group for further comment.

1. *Anaëric (anoxic) Anoxia*

This group comprises "*mal de montagne*" and *aviation anoxia* as the most important forms. Both may be termed *altitude anoxia.* The former was already described by the Jesuit priest Joseph de Acosta in 1588. The latter was already recognised as due to oxygen deprivation in the era of balloon flights long before the advent of aeroplanes. Paul Bert, Claude Bernard's successor as professor of physiology in Paris published his classical "La Pression Barométrique" in 1878. And in 1875 he had written a letter to Tissandier, Croce-Spinelli, and Sivel warning them, that the proposed oxygen supply for their last flight (three 150 liter bags of 72 % oxygen) was insufficient for their purpose. Unfortunately his letter did not reach them in time and two of them died from anoxia during this dramatic flight, from which we have the classical observations by Tissandier, the only one to survive.—The Englishman Glaisher had already 13 years before (1862) given a graphic description of anoxia during a flight (8833 metres). We note that both Glaisher and Tissandier, according to their careful notes, lost the full use of their limbs before they lost consciousness.

The enormous development of aviation since the first World War—both for peaceful and military purposes—has of course necessitated and stimulated the study of aviation medicine, in which neurological problems loom large,—first and foremost the problem of cerebral anoxia.

The oxygen tension decreases with the ascent to higher altitudes. At sea level the oxygen, constituting 20.96 % of the air, has a partial pressure of 159 mm.Hg. The alveolar air, saturated with water vapour (47 mm.Hg.) has correspondingly an oxygen tension of 103 mm.Hg. At an altitude of 12,500 feet the partial pressure of oxygen in the alveoli is reduced to 60 mm.Hg., at an altitude of 20,000 feet to 40 mm.Hg., at 25,000 feet to 30 mm. etc.[1] (cf. Armstrong).

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[1] For comparison it should be kept in mind that at sea level the partial pressure of oxygen in the alveoli is being reduced from 103 to about 40 mm.Hg. during the oxygenation of the blood, whilst the carbon dioxide partial pressure in the alveoli at the same time rises from about 40 to 46 mm.Hg.

As a consequence of this the oxygenation of the blood in the lungs also sinks with increasing altitude, although at first not so rapidly as the oxygen tension in the alveoli. A consequence of this again is a deficient oxygen supply to the cells and these will stop functioning and eventually be destroyed in the order of their vulnerability, as already mentioned (1. cells of cortex cerebri and of basal ganglia, 2. cerebellar cells, etc.).

At an altitude of about 25,000 feet unconsciousness occurs. But before then some subjective symptoms may be present such as sleepiness, headache, fatigue, euphoria, psychological impairment, but never pain,—on the other hand sometimes an abnormal sense of well-being. In his excellent and interesting book on Aviation Medicine *H. G. Armstrong* complains: "It is to be regretted that altitude sickness is not a most painful or disagreeable process. If it were, the health of flying personnel and the safety of aviation would be greatly enhanced." On the other hand the after-effects of flying hypo-oxia in the form of intractable headaches of varying duration seem to be frequent enough according to *Armstrong*. He also mentions the possibility that "a severe or prolonged hypo-oxia may affect the tissue cells" in such a way as to create a "histotoxic hypo-oxia", thus engendering a vicious circle.

Obviously the anoxic disturbance and damage will depend on the altitude, the length of time of exposure and the rate of ascent. (At a very rapid ascent to 30,000 feet, which is now possible with modern planes, a decompression syndrome—"divers' disease"—may occur and this may be very painful, which anoxia as a rule is not. Vestibular disturbances, caused by obstruction in one Eustachian tube is not part of the anoxic picture, nor are the vestibular illusions that may occur. But the evaluation of these may well be influenced by an anoxic state).

The prophylaxis and treatment for aviation anoxia consists of course in oxygen supply by means of a satisfactory mask *in good time* before symptoms occur. (By denitrogenation of the body this may also prevent decompression, when oxygen breathing starts early enough, preferably from the ground up, in rapid ascents. For very high flights *Armstrong* recommends pure oxygen breathing for a half to one hour prior to ascent).

Negligence in using the prophylactic oxygen supply in time has been attended by severe disturbances, even permanent disturbances and fatalities in a number of cases.

In this group should also be listed the anoxia caused by nitrous oxide anæsthesia without the necessary admixture of oxygen. Undiluted nitrous oxide is still used, in some countries at least, for very short anæsthesias (1 or 2 minutes); for longer periods of time it must be diluted with oxygen in sufficient quantity (20 %). [Even then it may perhaps be attended by a risk of cerebral complications, cfr. Skinhöj.]

2. *Obstruction Anoxia*

This group comprises all conditions where a constriction of the air passages for any reason has become so severe as to prevent a sufficient access of air to the alveoli or to stop it altogether. The cause may be a *corpus alienum*, stuck in the laryngo-pharynx (e.g. a too big piece of meat), diphtheric membranes, accumulation of secretion and fluids in *paralysis of the 9th and 10th cranial nerves* (as frequently seen in bulbar poliomyelitis), *myasthenic exhaustion* of the deglutition mechanism, laryngeal paralysis, preventing the rima glottidis from opening, pneumonia and pulmonary oedema, which latter conditions reduce both the efficacy and the extent of the alveolar respiratory surface, which normally amounts to about 90 square metres (90 m^2).

Drowning may also be listed here, although strictly speaking it is also due to absence of available oxygen in the surrounding matter (water) as well as to obstruction of the air passages, and might therefore logically better be referred to Group 7 (Mixed or combined anoxia).

In a case belonging to this group I have seen a healthy boy on account of acute anoxia reduced to a decerebrate existence, which lasted for nearly 5 years. I have described it in *Acta psychiatrica et neurologica Scandinavica* Vol. XXVII, 1952, Fasc. 1–2 and further details will be reported by my former assistents Drs. Lindahl and Lundervold.

A case like that gives food for reflection. When one hears of a case e.g. a case of drowning, in which it is announced that efforts at resuscitation "succeeded at last", one cannot help wondering if the success always constitutes "useful survival". I doubt it. Now this is not meant as a warning against efforts at resuscitation. Far from it. It is our duty to make our utmost efforts at resuscitation without beforehand speculating about the result. But it is also our duty to face the possibility that in spite of the apparently successful resuscitation, the anoxia may have brought about an invalidity which should not be overlooked.

From the above it will be seen that in *bulbar poliomyelitis* affection of some of the caudal cranial nerves in an *indirect* way may bring about respiratory difficulties where the respiratory failure is due to that accumulation of fluid and secretion blocking the respiratory passages which follows paralysis of these two cranial nerves. Here *postural drainage* is the treatment, which first and foremost has to be arranged for, preferably before any respiratory difficulties have manifested themselves. Consequently a careful examination of the cranial nerves by an experienced examiner is of very great importance for the establishment of the right treatment in time. This examination should cause the patient the least possible motor effort and should for this reason preferably be carried out by one experienced in such neurological examinations. (This is one of several reasons why neurological guidance from beginning to end is so important in the treatment of this disease). For the uninitiated the following manoeuvre may be useful: Ask the patient to blow up his cheeks. If he fails to make his cheeks bulge, pinch his nose, so as to prevent the air escaping through his nostrils. If he can *then* make his cheeks bulge, you know that the velum palati is already paretic, the motor domain of the 9th and 10th cranial nerves has already been invaded and respiratory trouble is already brewing.

In *myasthenia gravis,* as already mentioned, the same form of anoxia may be seen. Here also postural drainage is of great importance— and, of course, intravenous prostigmin injections.

In both conditions aspiration through a tracheal tube, perhaps after tracheotomy, may be necessary when accumulation of secretion and fluid have gone too far for postural drainage alone. When anoxia has gone so far as also to cause failure of respiratory centres, artificial respiration by means of a respirator will be necessary. But as primary treatment it will do no good, may even do harm, when the afore-mentioned accumulation of secretion is the primary cause: This must first be dealt with. There is here a great practical difference from the following form:

3. *Paralytic Anoxia*

This form is due to a primary failure of the diaphragm and the rest of the respiratory muscles, moving the respiratory "bellows" with sufficient power and coordination. This may be caused by paralysis or incoordination (as in spinal and/or bulbar poliomyelitis), in amyotrophic lateral sclerosis, spinal (C_4) or bulbar tumour and other affections involving respiratory centres or ant. grey horns, or by exhaustion as seen in myasthenia gravis. Here, of course, artificial respiration preferably by means of a respirator is first and foremost to be resorted to.

In a way the anoxia caused indirectly by paralysis of the 9th & 10th cranial nerves might also be called paralytic anoxia. But as for practical therapeutic reasons it is of great importance that these *indirectly* acting paralyses should not be treated in the same way as this primary paralytic anoxia, I consider it better for didactic reasons to use the classification which I have given here.

Also in this form arises the same question as dealt with under the previous group: viz. Is it always a fully "useful survival" we obtain when under these conditions we bring the patients through the anoxic period alive, or has he intellectually, emotionally, or in motor respect become more or less a permanent invalid as a result of the anoxia? This depends to a large extent on the time the rational treatment to prevent or counteract an increasing hypo-oxia has set in. Here as elsewhere in medicine an early treatment has infinitely better chances than one that sets in after a good deal of damage has already been done.

The paralysing influence of morphine on the respiratory centre in the medulla oblogata should be mentioned in connection with this group. Already 1 centigramme of morphine influences the respiration and renders the respiratory centre less sensitive to the normal stimulating effect of carbon dioxide. On purely empirical grounds already the physicians of former generations knew that Cheyne-Stokes respiration, the first warning of failing respiratory coordination (in its widest sense) was in itself a contraindication to morphine. (*Laache*). Subsequent experimental research has confirmed this empirical truth, as so many others.

Barbiturates have a similar action to that of morphine.

4. *Anemic Anoxia*

In this group it is the means of transportation that is failing. The oxygen is chiefly transported from the lungs to the tissues, chemically bound to the hemoglobin of the erythrocytes as oxy-hemoglobin.

There may be too few erythrocytes or too little hemoglobin,— or the hemoglobin may be bound to other chemical substances in combinations where the binding is firmer than it is in oxyhemoglobin.. A typical instance of this is the carbon monoxide "intoxication", which is only or chiefly an intoxication in the sense that it binds the hemoglobin in a firmer combination than does oxygen. Whether it has any toxic action besides is debatable. Possibly the occurrence of polyneuritis might be cited in favour of this.

Many years ago *Cecil* and *Oscar Vogt* stressed the frequency of lesions in the basal ganglia and particularly of the pallidal system in CO poisoning (cf. their term "pathoclise"). As CO gas has no smell, it may seize its victims in a surreptitious way; but it is also a relatively frequent means of suicide. The usual proceeding is to turn the gas on in a carefully closed room. The ordinary gas for lighting and heating purposes contains from 7 to 15 % CO. For comparison it should be mentioned that exhaust gas from internal combustion engines contain about 10 % and that gas from explosions may contain 34 % (dynamite) to 46 % (nitrocellulose).

Characteristic of the clinical picture is the bright red, "cherry-red" appearance of the victim, due to the bright red colour of the CO hemoglobin.

Although the CO hemoglobin is a much more firmly bound chemical compound than the oxy-hemoglobin, it is not a completely irreversible compound and the CO can be "aired out" by deep respiration.

This airing out is considerably accelerated by pure oxygen breathing and still more, when to the oxygen is added CO_2 (5–7 %). Inhalation of this "carbogen" for 1 to 3 hours should now be the routine treatment of acute CO poisoning, as stressed by *Vagn Zahle* in his monograph of 1948. Artificial respiration may be needed. Coramin-cardiazol medication may be tried. Methylene-blue, which has been recommended should according to *Haggard & Greenberg* be warned against as "a synergist, not an antidote, for carbon monoxide". It may lead to the formation of methemoglobin.

Worster Drought et alii have described a *methemoglobinemia* of hereditary occurrence, the ensuing hypo-oxia of which they think capable of causing neurological disturbances.

5. *Stagnant Anoxia*

This group, due to circulatory insufficiency or stoppage, may be divided into two groups:

I. a group, comprising all cases due to *general* insufficiency of circulation, mostly of cardiac origin, and

II. all the cases in which there is a *local* circulatory insufficiency or stoppage, —also called *ischemia*. This may be due to thrombosis, to embolism or to pressure on a particular blood vessel or a particular group of vessels. *Courville*, in recent times the one who has more than anybody drawn our attention to the wide occurrence of anoxia as a pathogenetic factor, rightly calls *ischemia "the limited alter ego of anoxia"*. In the usual vascular catastrophes in the brain (hæmorrhage, embolism, thrombosis) local anoxia is probably a principal pathogenetic factor.

In *trauma capitis* intracranial oedema and hæmorrhages may exert such a pressure on the blood vessels as to cause a considerable hypo-oxia besides other pathogenetic factors which I shall not enter upon here.

In severe *cardiac insufficiency* pronounced hypo-oxia is a frequent occurrence, here as a rule accompanied by hypercapnia, which by its stimulating action on the respiratory centre is to a great extent responsible both for hyperpnoea and the accompanying conscious air hunger which together with the hyperpnoea constitutes the symptom dyspnoea.

In *cardiac surgery* stagnant anoxia constitutes a great danger. Also here the important question of useful survival has to be taken into account. Artificial lowering of the body temperature may here be useful by increasing the tolerance of the cells to anoxia.

In a case of Adams-Stokes disease, due to incomplete block of the atrio-ventricular bundle which with my late teacher, Professor *P. F. Holst,* I described in 1911 (*Quarterly Journal of Medicine,* Vol. 14, no. 16) brief spells of unconsciousness sometimes accompanied by light convulsions, occurred when the cardiac rhythm changed from the usual ventricular bradycardia to a much quicker rhythm, as at times it did, —probably accompanied by pronounced hypo-oxia, responsible for both spasms and unconsciousness,—as retrospective reasoning has lead me to believe.

In this connection I should like to mention *Tournay*'s very interesting observation of an extensor response during the apnoeic phase in Cheyne-Stokes respiration. (*Revue neurologique* 1927, I, 356–358).

Before we leave the group of stagnant anoxia *strangulation* must also be briefly mentioned. The chief—and at any rate the first –factor in strangulation is compression of the carotids and the vertebral arteries, even if the larynx or/and trachea may also be crushed. Some strangulation experiments in man here claim our attention: By a specially designed pressure cuff applied to the lower cervical region, abolishing the blood supply to the carotid and vertebral arteries without restricting respiration. *Rossen, Kabat* and *Anderson* produced an almost instantaneous complete cerebral anoxia, experimenting on normal young subjects (for periods up to 10 seconds), and on schizophrenic patients (for periods up to 100 seconds). Of their findings I may just mention the following points (after *Steegman*'s rendering of the original article): Loss of consciousness took place in 6 to 10 seconds. It was followed by a generalized tonic clonic convulsion of 6 to 8 seconds' duration. This occurred after the pressure cuff was released upon the beginning of unconsciousness, during which the EEG showed large slow waves.

After the return of consciousness the subject would show a variable reaction for 15 to 20 seconds. This was described as a confused, dazed, excited, euphoric, or fearful state. Abdominal reflexes disappeared only after prolonged anoxia and reappeared more slowly than the corneals. Extensor plantar reflex response was noted in some cases.

After releasing the cuff, thus restoring the cerebral blood flow, flushing of the face preceded the return of consciousness.

All the preceding forms of anoxia might well be termed anoxemia or hypoxemia, inasmuch as the blood does not transport sufficient oxygen at the necessary rate of supply to the tissues. Apart from CO poisoning, showing a bright red appearance and the pallor of extreme anemic conditions, they mostly present a cyanotic appearance, due to the prevalence of reduced hemoglobin, which in contradistinction to oxyhemoglobin has a dark colour, as has also methæmoglobin. Cyanosis is therefore an indication of lack of oxy-hæmoglobin in the circulating blood and has nothing to do with hypercapnia.

6. *Histotoxic Anoxia*

In this group there is no anoxemia. The blood carries enough oxygen at a satisfactory rate; but the cells are not in a position to utilize the oxygen brought to them. The classical form of anoxia in this group is cyanide poisoning. It generally runs a short and drastic course ending fatally in a very short time (from less than a minute up to an hour or more). Hyperpnoea and initial convulsions are succeeded by failure of respiration, loss of consciousness, and death. As the oxyhæmoglobin of the blood is not reduced to hæmoglobin, there is no cyanosis and the contrast between the bright complexion of the patient and the failing respiration is of diagnostic importance. Lavage of the stomach, intravenous injections of sodium nitrite (5 cc. of 1 % solution) or methylene blue (35 cc. of 1 %) which is supposed to cause the formation of methæmoglobin, which inactivates hydrocyanic acid, should be tried and may be of some use, if applied early enough. Artificial respiration and inhalation of 5–10 % CO_2 in 90–95 % oxygen should be tried if respiration ceases. (The lethal dose of hydrocyanic acid (HCN) for an adult person of 70 kg. body weight is 5–25 centigrammes, of sodium cyanide (NaCN) 10–45 cg. and of potassium cyanide (KCN) 12–60 cg.)

Hartman has suggested that cerebral concussion may cause a histotoxic anoxia in a mechanical (traumatic) way, in addition to and preceeding the anoxia, caused by pressure on blood vessels by intracranial traumatic oedema, which I have already mentioned under the group of stagnant anoxia. If this be right, we have here already entered the field of anoxia arising from various, pathogenetically different causes viz.

7. *Mixed or Combined Forms of Anoxia*

Nearly every one of the above-mentioned forms may combine with one or more of the other forms. It has also been suggested by *Courville* that if any case of anoxia belonging to one of the first five groups has lasted long enough a secondary histotoxic anoxia will arise as a consequence—and as a link in a vicious circle, accelerating the development of anoxia.

The chief member of this group, however, is *Encephalopathia infantilis* (sometimes by a misnomer called "Cerebral Palsy"), where no doubt anosmia plays an important rôle, particularly in those cases in which the damage has been done during birth, during the transition from placentar to pulmonar respiration. Whether anoxia during birth or mechanical trauma here is the most frequent principal cause, is a question upon which opinions are still divided; but there can be no doubt about the risk of anoxia arising from a too long interval between the cessation of the placentar and the start of the pulmonary respiration. Breech presentation in this respect represents a greater risk than head presentation. All complications involving the placenta and/or the umbilical cord may cause a stagnant anoxia, this again may cause respiratory movements before the head is delivered, thus creating an anaëric anoxia, followed by an obstructional anoxia, a combination of 5, 1, and 2, according to the above-mentioned pathogenetic grouping of the different forms of anoxia. If analgesics, anæsthetics, or sedatives be given the mother during birth, this additional factor, making for anoxia, may be "the straw that breaks the camel's back" (*sit venia verbo!*).

As, however, another reporter is going to deal with this topic separately, I shall not enter into details in this field. Only let me refer to *Windle & Becker*'s experimental study in pregnant guinea pigs, in which after clamping the uterine vessels on the umbilical cords of some members of a litter they have observed interesting behavioural differences and reduced learning ability (maze studies) in those members of the litters that had been exposed to this experimental anoxia. These findings, besides the accompanying neuropathological study, make this publication particularly interesting from the neuropsychiatric point of view. (*American Journal of Obstetrics and Gynecology,* Vol. 45, no. 2, Febr. 1943). It throws an interesting light on the imbecile forms of encephalopathia infantilis. Let it finally only be mentioned that anoxia also may be the principal causative factor of the other forms of this large and clinically heterogenous group of conditions such as the spastic form (described by *Little* in 1843 and often called Little's disease), the choreo-athetotic form, the epileptic form, and the quite frequent mixed forms.

In the foregoing survey of the different pathogenetic forms of anoxia I have chiefly dealt with conditions under which the anoxic factor has been overwhelming,—if not strictly speaking the only,—etiological factor,—"anoxia major", if you like.

We have still to talk of "anoxia minor" i.e. that milder hypo-oxia, which needs much longer time to exert its pathogenetic action.

Besides, we have also the following important question, that must be touched upon, if not fully discussed:

1. Can an acute severe anoxia not only cause permanent disturbances, but also give rise to progressive lesions?
   In this connection some problems of epilepsy have to be mentioned.
2. Can neurological affections of hitherto unknown etiology find their etiological explanation by anoxia or hypo-oxia?
3. Can our knowledge of anoxia throw new light on the problems of "psychoneuroses"?

Based on extensive neuropathological study of a great number of cases *Courville* has shown that the permanent lesions caused by a sufficiently strong acute anoxia (the result of the irreversible anoxic changes) may have a tendency towards progression, due to endothelial proliferation with occlusion of blood vessels, partly also due to glia proliferation, and possibly also to deformities caused by extensive atrophy and cicatricial shrinkage.

That anoxia and in particular natal anoxia may be a principal cause for *epileptic states,* must be regarded as fairly well established by now. It tallies quite well with the views of *Foerster,* who considered birth trauma to be one of the principal causes of epilepsy.

Earle, Baldwin and *Penfield* in 1952 described a condition which they call "incisural sclerosis" and consider due to a herniation of the temporal lobe during birth resulting in occlusion of vessels, ischemia, i.e. anoxia of certain parts of the temporal lobe, where necrosis of ganglion cells and a gliotic scar formation lead to the clinical picture of "temporal lobe epilepsy."

If epilepsy in its various manifestations thus may be a consequence of anoxia, it should also be kept in mind that every *convulsive seizure* combined with pronounced *cyanosis* in itself represents an anoxic episode which, if strong and long enough, may cause additional permanent cerebral damage, establishing thus a vicious circle.

As regards *"anoxia minor", the mild chronic hypo-oxia* which will only have a pathogenic effect when present over a longer period, the situation is much more complicated and other possible factors such as hypercapnia, hypoglycemia, accumulation of metabolites may also enter into the causation and make our judgment regarding the rôle of the hypo-oxia difficult.

Four authors (*Scheinberg, Blackburn, Rich* and *Saslaw, Arch. Neurol. & Psychiat.* July 1953) have found a reduction of the cerebral circulation with increasing age, particularly noticeable after 50, the cerebral vessels being narrowed by sclerotic changes and/or contraction of the vessel walls. The resulting chronic hypo-oxia *may* be one of the causes of the ensuing *"subclinical vascular encephalopathy in the aged"* —possibly even the principal one, but probably there is a conflux of a number of causative factors.

What about *multiple sclerosis?*

Aird some years ago thought that the frequent fluctuations in this disease—in particular the rapid ameliorations—pointed to "abnormal physiology without abnormal pathology" (*Neurology* 1951 May-June), probably caused by "deficient oxygenation". *Courville,* on the other hand, has on my inquiry been very much reserved as regards this possibility.

Personally I find it somewhat strange if anoxia, which first and foremost affects the cells, should be the cause—or one of the causes of this demyelinating disease. If, however, an affection of the oligodendrocytes be the cause of demyelination, as *Lumsden* thinks, it would be a question, how vulnerable the oligodendrocytes are to hypo-oxia. The same applies to other demyelinating diseases, such as encephalitis periaxialis diffusa (*Schilder*) and the acute infantile form of "diffuse sclerosis" (*Krabbe*).

These few examples will have to suffice. We live in the era of "conditionalism" as regards etiology: one etiological factor often needing one or more cooperative other factors to effect a lesion and a disturbance. Possibly and probably hypo-oxia with *episodic exacerbations to anoxia,* local or general (??), may be a member of "the etiological band" with a number of conditions not mentioned here. Future research will show.

Finally we have as briefly as possible to discuss the possibility of a relation between anoxia and the so-called *functional nervous disorders,* including also the *psychoneuroses.* Is there any relation? Can our knowledge about anoxia in any way throw light on the psychoneurotic problems?

In our present "psychosomatic" era ("psychosomatic" being a good new name for an old point of view, in practice better known to the old family doctor than to the modern specialist) we hear a great deal of "psychosomatic" disturbances, where causative psychic factors have produced bodily ailments. We hear considerably less about "somato-psychic" ailments,—where somatic lesions produce psychic peculiarities and ailments.—These, however, are probably quite as important.—

Looking back on the development of neurology during the time of the last century, one will notice, that quite a number of ailments have been transferred from the so-called functional neuroses to the group of somatically conditioned, "organic" nervous disorders. This is mostly due to the more systematic clinical examination, aided to newer auxiliary methods and to the development of neuropathology and experimental research. Now there is no reason to believe that this development has come to an end. On the contrary there is every reason to assume that it will continue. (Perhaps in this connection I may be allowed to refer to a short neurophilosophical article of mine in *Journal of Mental Science,* April 1921, entitled "On the possibility of a biological conception of so-called functional nervous disorders".)—

When we consider anoxia in this connection, we should first and foremost bear in mind that the acute anoxia regularly is accompanied by psychic peculiarities and disturbances, such as confusion, emotional disturbances, euphoric excitation, fear, etc. In his excellent survey of the "Clinical Aspect of Cerebral Anoxia in Man" (*Neurology* July-August 1951) *Steegman* writes: Peculiar emotional changes materialize and so closely resemble hysteria that erroneous diagnosis is frequently made. Emotional lability, screaming, laughing, crying or intervals of apprehension and fear characterize this stage."—

Now most of these psychic disturbances are probably transitory. But in anoxia, where reversible and irreversible changes may exist side by side, it is quite feasible—indeed, probable even, that in some cases just those changes remain permanent which are responsible for all or some of these psychic peculiarities and disturbances.

In the *Mott Memorial Book* of 1929 (H. K. Lewis & Co., London) *F. A. Pickworth* has under the title of "Mental Disorder and Deficient Oxidation" collected a number of observations which point in the same direction.

We know, then, that anoxia may produce transitory "somato-psychic" disturbances. Some of these probably remain permanent in certain cases, just as most other anoxic lesions and disturbances may. Future research will have to try to determine to what extent the factor of anoxia is active in the etiology of the functional neuroses, including the psychoneuroses.

In what precedes I have tried to give a rough survey of the clinical aspect of cerebral anoxia, of which I have only managed to bring in few details and rather sporadic exemplification.

I venture to hope, however, that this survey has sufficed to give an impression of what a vast topic anoxia is, and what an important rôle anoxia plays in clinical medicine today. In the future it will certainly play an even greater rôle.

To sum up then:

The acute "major anoxia" and its consequences are known fairly well, although there may be some doubt about the frequency of the permanent and progressive sequelae.

The chronic "minor anoxia", a long-lasting milder hypo-oxia,—possibly and probably with episodic excerbations—we know less well.—

A great deal of very valuable research has been done in this field ever since the time of *Paul Bert*. But future research—both clinical and anatomical and physiological—still has numerous problems to solve in connection with anoxia, as I have tried to point out.—

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BRAIN-STEM ENCEPHALITIS AND EPIDEMIC VERTIGO

By

FOLKE MÖLLER

Apart from certain inflammatory nervous diseases, which nowadays can be more or less affirmed etiologically, there remains a group of non-purulent inflammations in the nervous system whose etiology is still unknown. Owing to their benign course and to the absence of pathologic-anatomic observations, their pathogenesis is also wrapt in obscurity. Therefore, the diagnosis and classification becomes dependent on the guidance of the clinical picture. It is possible, indeed even probable that they are manifestations of etiologically and pathogenetically different diseases. One group, however, due to its clinically well demarcated picture, is clearly distinguishable from the others; it appears in the form of paresis of the cranial nerves which issue from the brain-stem. For reasons previously reported (1, 2) I am of the opinion that the injury in most of these cases is centrally situated, and have therefore called the disease brain-stem encephalitis. A new series of cases of this malady is to be discussed in the following for two reasons, partly to make a new contribution towards the troublesome symptomatology of brain-stem encephalitis, and partly to point out anew that many cases of vertigo, and especially those of epidemic appearance, are none other than a special form of lower brain-stem encephalitis.

Table 1 is a survey of non-purulent inflammation in the nervous system observed within the last six years at this hospital. As seen, cases of brain-stem encephalitis comprise over 40 % of the whole material[1].

As previously, the patients came from the glen of the Ångermanälv and its feeder-streams. It is therefore less of an epidemic than of an endemic nature of several years' standing, without predilection for any particular time of the year. If cases of brain-stem encephalitis

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[1] The figure is higher than in 2 earlier series (about 20 %) because the number of children in the present material is inconsiderable, and encephalitis after specific infectious diseases is not included. A number of poliomyelitis cases without paresis are probably concealed among cases of meningitis.

TABLE 1

Cases of non-purulent inflammation in the nervous system at the Army Hospital, Nov. 1948–Dec. 1954. Nervous complications after specific infectious diseases and poliomyelitis with paresis not included. Classification accord. to Möller 1949.

Diffuse cerebral involvement of brief duration ...	2	cases
Hemiplegic syndrome ...	3	–
Dominating mental symptoms ...	4	–
Encephalitis of the upper brain-stem ...	1	case
Encephalitis of the lower brain-stem ...	39	cases
Encephalomyelitis ...	4	–
Polyradiculoneuritis ...	13	–
Meningitis ...	23	–
Miscellaneous ...	1	case
Total	90	cases

TABLE 2

Serological investigations of 25 cases of encephalitis of the lower brain-stem. Some samples were examined at the State Bacteriological Laboratory and others at the Sahlgrenska Bacteriological Laboratory.

	neg.	pos. ?	pos.	Total
Blood				
Bacterial culture ...	19	0	1[1]	20
Agglutination (Salmonella Brucella Bang Tularaemia) ...	21	0	0	21
– (Leptospirosis) ...	21	0	0	21
– (Influenza B) ...	2	0	0	2
– (Paul-Bunnel) ...	2	0	0	2
Complement-fixation (increased antibody titre)				
(Toxoplasmosis)	9	1	0	10
(Mumps) ...	14	3	0	17
(Herpes) ...	9	1	0	10
Neutralizing antibodies (Herpes) ...	2	0	8	10
Antistreptolysin titre[2] ...	14	–	7	21
Cerebrospinal fluid				
Isolation of virus (mice) ...	10	–	0	10
Feces				
Isolation of virus (mice) ...	10	–	0	10
Isolation of Coxsackie virus (mice) ...	6	–	0	6

[1] α-streptococci.
[2] >200 IU/ml = pos.

only are taken into consideration, they mostly originate from the towns Kramfors, Sollefteå and intervening districts on both sides of the river, with a stray case here and there from the countryside north of Sollefteå. The frequency has varied from year to year. About 60 % of the whole material were between 20 and 49 years of age (of brain-stem encephalitis close upon 80 %). The number of men was larger than the number of women, even in consideration of the military element of the hospital.

The general clinical symptoms revealed by this encephalitis were fairly similar. A few days, one or two weeks after a common cold, the patient had headache, sometimes as diffuse pressure, but for the most part as throbbing pain behind and around the eyes, with nausea or vomiting. Afterwards the focal symptoms manifested themselves rather quickly. Preceding infection was often missing and the focal symptom appeared as the first sign of the disease. Headache was seldom absent. It was of a temporary nature. Some of the patients had fever, but it was then only inconsiderable. SR was normal or slightly enhanced, the latter probably as a result of foregoing infection. The cerebrospinal fluid was normal or showed mild pleocytosis. It was not unusual that the focal symptoms decreased during the first days and then increased. A fluctuating course of this kind was especially common in vertigo, which frequently disappeared as quickly as it appeared, and soon returned with increased intensity. The course was benign, and half the number of patients could be dismissed from the hospital after one month at the most. Both the milder and medium-difficult types of paresis, as well as conditions of insufficiency, could proceed for several months. This was especially the case as regards occasional patients with facial and cochlear paresis also with recurrent paresis. Four patients had earlier suffered from a similar complaint. In my experience such recurrences are not unusual in brain-stem encephalitis.

Attempts were made to arrive at an etiological diagnosis by sending samples from patients to be bacteriologically, serologically and virologically examined. Unfortunately systematic investigation was impossible. Fifteen cases were not examined, the remaining 25 only partly. The latter are included in Table 2. The rest, as seen, were on the whole negative, apart from the enhanced antistreptolysin titre in some cases —probably an expression of the foregoing infection.

The neurological symptomatology of brain-stem encephalitis is of special interest. The distribution of the 40 cases is as follows:

Paresis of one cranial nerve	17	cases
Paresis of two or more cranial nerves	7	–
Vertigo, simple	12	
Vertigo with simultaneous paresis of other cranial nerves than the vestibular nerve	4	–
Total	40	cases

Apart from two cases of dissociated paresis of conjugate movement all the cases of cranial nerve paresis were unilateral. When several cranial nerves were injured the paresis was on the same side. The separate cranial nerves were injured in the following manner:

IIIrd nerve	1 case
Vth nerve	5 cases
VIth nerve	4 –
VIIth nerve	14 –
VIIIth nerve (vestibular)	5 –
– – (cochlear)	6 –
Xth nerve (recurrent)	2 –
XIIth nerve	1 case
Paresis of conjugate movement	2 cases
Horner's syndrome	1 case
Cerebellum	1 –
Vertigo with normal caloric reaction	11 cases

The following is brief commentaries on these cases:

14 cases of paresis of the VIIth nerve. Three were of the common peripheral type, but only in one was the taste reduced. A further 5 cases of simple facial paresis, while under observation, manifested certain peculiarities: In one, the paresis in the upper branch was only partial. In another, iridocyclitis with simultaneous sarcoidosis (?). One patient had previously had positional nystagmus, and one an earlier contralateral facial paresis also recurrent vertigo. The last of the five patients, who now suffered partially from the Melkersson syndrome, had already had contralateral facial paresis in combination with paresis of the trigeminal nerve. In the remaining 8 cases facial paresis was combined with paresis of other cranial nerves. The combinations were: In two cases the Vth and VIIth nerve, in one, the VIIth and VIIIth (cochlearis), in one, the VIIth + dissociated paresis of conjugate movement and in the last case, the VIIth (lower branch) + Vth + VIth + palatal paresis + nystagmus. Of these 14 cases of paresis of the VIIth nerve, 4 had reduced taste, 8 had none, and no tests were made in two cases. One patient had paresis of the lower branch only, with three it was preponderant in this branch, whereas in the remainder of the cases both branches were affected to about the same degree.

5 cases of paresis of the Vth nerve. Two of these were simple and three combined (2 with the VIIth nerve and one with the VIth and VIIth + palatal paresis + nystagmus[1]). The expansion of sensibility disturbance was of great interest. Whereas 2 of the 5 cases displayed a type which more or less followed the spread of the trigeminus branches, 3 were of bulbiform distribution, which characterizes the central origin, in one case only subjectively as facial paresthesia, but "objectively" demonstrable as hypalgesia of the palate. Fig. 1 illustrates the spreading in such a case. The sense of temperature in 2 of the last mentioned cases, where this was tested, was not diminished.

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[1] Apicitis could be excluded.

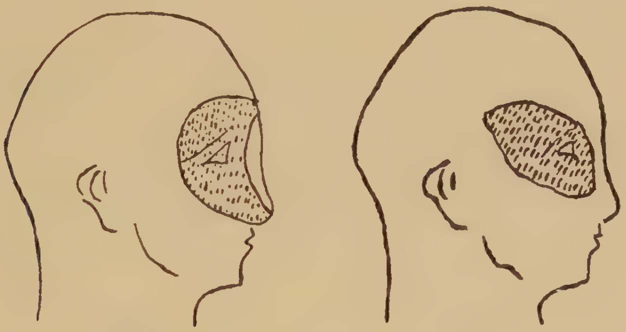
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Fig. 1.

4 cases of paresis of the VIth nerve. One of these was simple, the others were combined with (1) positional vertigo (2) Horner's syndrome, and (3) simultaneous paresis of the Vth and VIIth nerves, also palate + nystagmus.

2 cases of paresis of conjugate movement. Both were of the dissociated internuclear type.

The course was as follows:

Case H. (1) Paresis of conjugate movement to both sides and upwards. On attempt to deviate to the sides, nystagmus of the abducing eye, on attempt to deviate upwards, bilateral vertical nystagmus.

(2) Paresis of conjugate movement to the right diminished. Bilateral nystagmus on deviation to the right.

(3) Slight paresis of the abduction and adduction of the right eye.

(4) Disappearance of paresis and nystagmus.

The convergence was not tested. Caloric irritability normal as regards tendency to fall and faulty pointing. The nystagmus was difficult to judge owing to the paresis.

Case J. (1) Paresis of abduction and adduction right, also of adduction left. Thus, paresis of conjugate movement to the right + adductor paresis right.

(2) Paresis of abduction and adduction left and of abduction right. Thus paresis of conjugate movement to the right + abductor paresis left.

(3) Slight paresis still present. Normal convergence. Caloric reaction normal. No nystagmus.

Accordingly, here were cases of dissociated paresis of conjugate movement of the form which appears in connection with injury to the dorsal longitudinal fasciculus.

One case of paresis of the IIIrd nerve. The only symptom: unilateral ptosis.

6 cases of paresis of the cochlear nerve. Unilateral neurogenous deafness, in every case preceded by tinnitus. Three were simple. Of the remaining 3, one was combined with homolateral facial paresis, while 2 simultaneously suffered from vertigo. This was of a very mild form in one of the cases, but was accompanied by paresis of the vestibular nerve on the affected side. The dizziness was severe in the other case, but the vestibular nerves reacted normally.

2 cases of paresis of the recurrent nerve. One of the patients had mild paresis of the palate, tongue and sternomastoid muscle, at the same time, on the same side.

16 cases of vertigo. Of these 12 were simple, and 4 were combined with paresis of other cranial nerves, i.e. two with the cochlear, one with the VIIth and one with the VIth nerve. Eight patients had rotatory dizziness, but this was less determinable in the others. The caloric investigation of the vestibular function revealed:

Normal labyrinths	11	cases
Unilateral labyrinth injury	4	–
Not tested	1	case
Total	16	cases

More remarkable cerebellar attributes (asynergia, dysarthria, normal vestibularis nerve) occurred only in one case. Spontaneous nystagmus developed in 13 of the 16 cases, for the most part independently of position.

DISCUSSION

I am aware that this series, like the foregoing one, cannot be quite homogeneous either etiologically or clinically. It is not always possible to distinguish clinically between central and peripheral injury. Among the cases of paralysis of the VIIth nerve there are probably some which are ordinary facialis-"neuritis" and, as regards vertigo, a case of neuritis of the VIIIth nerve may perhaps be met with here and there. Vertigo of the Ménière type has been excluded as far as possible. The following reasons argue, however, that in the preponderant number of cases the question concerns focal lesion in the lower brain-stem.

(1) The injury is unilateral, even when several nerves are affected. One exception to this rule is the bilateral paresis of such nuclei and tracts which lie in the vicinity of the median line. (VIth nerve, posterior longitudinal fasciculus). Divergently, neuritis and radiculitis, as is well-known, often cause bilateral, symmetric paresis.

(2) The expansion of paresis is in several cases of the type which occurs in connection with central, nuclear, or internuclear injuries and not as in cases of injury to nerve-fibres. Affirmative of the same is the diffusion of sensibility disturbance that characterizes affection of the descending root, as in the two cases of paresis of the Vth nerve mentioned above, and also dissociated paresis of conjugate movement, which is a sign of injury to the posterior longitudinal fasciculus. There are even other types of paresis which indicate nuclear or paranuclear genesis. They are frequently characteristic by only partially affecting the nerve-function. For instance, of the Xth nerve, only the function of the vocal chord is paralyzed, of the IIIrd nerve, in one case, only the function of m. levator palpebrae, of the VIIth nerve in several cases, the lower branch function preponderantly, of the VIIIth nerve, often either the cochlear or vestibular nerve[1].

Hence the injury is not located in nerve fibres, but is nuclear, paranuclear or internuclear.

(3) Mild symptoms from other conduction tracts occurred to a large extent and especially indications from the pyramidal tract. They were perceptible in 5 of the 12 cases, among others, with simple vertigo.

In a previously published series vertigo was the commonest clinical symptom, and even in this material the vertigo cases were relatively frequent (16 of 40). They differed neither regarding their epidemiological behaviour nor as to their clinical course from the other cases. Like these, they were often combined with symptoms from other nerves and tracts, namely:

---

[1] My colleague in ophthalmology has recently observed some cases of isolated, partial Horner's syndrome (ptosis, and miosis without enophthalmus (3)).

Vestibular symptoms only	8	cases
Vestibular symptoms + paresis of cranial nerves	4	–
Vestibular symptoms + symptoms from the pyramidal tract	3	–
Cerebellar symptoms + signs from the pyramidal tract	1	case
Total	16	cases

Half of the vertigo cases were thus combined with other neurological symptoms.

One asks oneself if this peculiar form of encephalitis which has been observed endemically in these tracts without any greater interruption since 1937, is characteristic of this region. Study of the literature indicates that such is not the case, for descriptions of "epidemic vertigo", published more recently (4, 5, 6) include among the described cases, not only simple vertigo, but also vertigo combined with paresis of the cranial nerves, and chiefly ophthalmoplegia. They must be looked upon and have also been apprehended by the authors as cases of encephalitis. The development of electroencephalographic disturbance during the course of the disease (7) also argues for such an assumption[1].

These experiences lead to the conclusion that *epidemic vertigo is only one of the many symptoms under which encephalitis of the lower brain-stem can manifest itself.*

In regard to the pathology one can only put forward assumptions. It must be a question of exceedingly small, in most cases solitary foci, much smaller and more delimited than those seen in vascular injuries, and with a good healing capacity. The appearance in many cases in connection with an infectious disease argues for the inflammatory or allergic genesis of the process. Immunity is imperfect as recurrences are not infrequent.

SUMMARY

1. Of the cases of encephalitis under observation during the last 6 years, 40 with symptoms from the lower cranial nerves have been studied.

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[1] Only one of our cases of brain-stem encephalitis was investigated electroencephalographically. It revealed paroxysms of delta-theta waves as well as sharp waves above both temporal regions, sometimes synchronous and sometimes more above the left or the right side. Changes for the most part had receded. (Dr. Dyrssen).

2. Similarities of an epidemiological, general-clinical and neurological character justify their classification as a nosological unit.

3. The neurological finds argue that the injury, in most cases, is localized in the lower brain-stem.

4. Vertigo is the commonest symptom, both with and without other neurological symptoms. "Epidemic vertigo" may therefore be regarded as a form of encephalitis of the lower brain-stem.

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Lund, M. (Odense, Denmark): Myasthenia Gravis in a Three Year Old Child.

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INTRODUCTION

The 13th Scandinavian Congress of Neurologists was held in Lund, Sweden, on June 6th–8th, 1955. The University of Lund was the first meeting-place of Scandinavian congresses outside the capitals.

111 active members were present, including neurologists from all the 5 Scandinavian countries.

Honorary members were Professor N. Antoni, Professor G. H. Monrad-Krohn, and Chief Physician K. H. Krabbe.

The Congress was inaugurated in the aula of the University in the presence of the Rector of the University of Lund, Professor Ragnar Bergendal, Professor A. Lindau, and Professor G. Petrén, besides the honorary members Monrad-Krohn and Krabbe. Professor Antoni was prevented from attending.

The opening address was delivered by the President of the Congress, Professor G. Wohlfart. Furthermore, Professor Bergendal and Professor Lindau addressed the audience.

The Lund Students' Choral Society entertained the audience with songs from the Scandinavian countries.

The meetings were held at Akademiska Föreningen, where there were also scientific exhibitions.

The main subject was: Anoxia cerebri. Introductory lectures were given by Professor M. Fog, Dr. Erna Christensen, Professor Monrad-Krohn, Dr. E. Nilsson, Dr. Ole Berg, Dr. Stig Tejning and Drs. Rooth & Sjöstedt. The main subject was treated from various points of view in a number of lectures, and afterwards there were discussions. Furthermore, lectures on various subjects were given in three Sections.

Telegraphic greetings were received from Professors Antoni and Munch-Petersen, and answers were returned.

The general meeting was held on June 7th, 75 members being present. Chief Physician Krabbe was in the chair.

An invitation was submitted by Professor Kaila that the next congress be held at Helsingfors in 1958. This invitation was accepted with gratitude.

The social programme included a reception on June 5th, a lunch at Akademiska Föreningen on June 6th on the invitation of the City of Lund, with addresses by Mr. Torsten André and Professor Monrad-Krohn. On June 7th a lunch was given at the University Hospital in Lund on the invitation of the Board of Directors and with addresses by Professor Gunnar Wiberg and Professor E. Busch.

On June 7th there was a banquet with 115 participants at Akademiska Föreningen. Addresses were delivered by Professor Gunnar Wohlfart, Dr. Knud Krabbe, Dr. Knud Winther, Professor M. Fog, and Professor Bergendal. After the dinner there was a special musical entertainment by two members of the Students' Choral Society, the well-known "Spex" of Lund.

After an excursion to Östarp in the afternoon of June 8th, the Congress ended.

A ladies' committee arranged a visit to the Museum of Cultural History and to the castle of Torup, furthermore, a lunch at Lund and a visit to Leo Ltd., the pharmaceutical firm at Hälsingborg (with a lunch given by Leo Ltd.).

Docent Bengt Lindegård was Secretary to the Congress.

KNUD WINTHER
Secretary-General,
Scandinavian Neurological Association

Cerebral Anoxia

PATHOPHYSIOLOGY

(Summarized)

By

MOGENS FOG
Copenhagen, Denmark

Nearly ever since Lavoisier's discovery of oxygen, it has been a well established observation that lack of this gas will cause severe cerebral damage with immediate and long-lasting symptoms. The understanding, however, of the pathophysiological mechanisms which determine cerebral lesions during anoxia and hypoxia has only developed with growing insight into the physiology of oxygen intake, oxygen transportation, oxygen diffusion from blood to tissue and the oxidation in the cells. It has not yet been possible to bridge to the full extent the gap between our physiological knowledge on the one hand and pathological observations on the other. Further progress in this field will demand thorough insight into the detailed pathophysiological conditions in various forms of anoxia and their relationship to the different pathological changes of brain tissue.

Neurologists have to some degree neglected these problems, while they have occupied the minds of for example the anesthesiologists intensely. On the other hand, some neurologists have recently become inclined to ascribe to anoxia a long range of diseases, especially in early years of life, which were until now regarded as degenerative or hereditary.

It is in the light of this state of things that we have chosen cerebral anoxia as the chief subject of our congress. It is the more important because advanced comprehension of the pathogenesis of cerebral anoxia may lead to effective preventive measures.

Anoxia (in what follows the term will comprise hypoxia as well) means that tissues do not receive a sufficient supply of oxygen to maintain the normal oxidation *or* that the tissue-cells for some reason are unable to utilize a normal supply, offer, of oxygen.

If the term *asphyxia* is to be upheld, it should be confined to mean suffocation: a sudden or progressive stop of respiration. Anoxia is only one of the consequences of asphyxia; increase of carbon dioxide content in the blood and different reflexes are others.

Ischemia stands for reduced or abolished circulation in a limited region. Here also anoxia is only one among several reactions which influence the tissue.

It is conceivable that these three different conditions will provoke different pathophysiological and pathological phenomena, but as far as I know, an elucidating correlative study in this field has not been presented so far.

Some elementary physiological dates and definitions must be kept in mind when dealing with our subject.

Volume per cent. of a gas in a fluid means the amount of cc. of the gas which can be physically absorbed or chemically combined—or both—in 100 cc. of the fluid.

The *oxygen capacity* of blood is the amount of cc. oxygen which can maximally be combined to hemoglobinia in 100 cc blood.

The *oxygen saturation* of blood is the amount of oxygen which in a given situation is actually contained in a sample, expressed as per cent. of the oxygen capacity of the sample.

The *tension* (*partial tension*) of oxygen means the pressure which oxygen must exert in the air above a blood sample to maintain equilibrium with the content in the fluid. It is identical with its percentage contribution to the collected gas pressure on the fluid.

In the alveoles the tension of oxygen is 110 mm/hg. In the blood only a negligible amount is physically absorbed, while hemoglobin. will combine with 1.34 cc oxygen per 1 g hemoglobin. The volume per cent. is then normally 19 cc., the tension 100 mm. In the capillaries oxyhemoglobin is reduced to hemoglobin, which is less acid than oxyhemoglobin. It therefore facilitates the liberation of carbon dioxide which in turn facilitates the dissociation of oxyhemoglobin.

In venous blood the volume per cent. of oxygen is reduced to 14 under normal conditions, the tension to 40 mm, the saturation lowered from 95 to about 70 per cent, while the volume per cent. of carbon dioxide is raised from 50 in arterial to 56 in venous blood, the tension from 40 to 46 mm/hg.

The respiratory quotient of the brain, (the relation betwen volumes of CO_2 produced and volumes of O_2 absorbed) is 1 because glucose is the main source of cerebral metabolism. The effect of anoxia on the brain therefore in the first place depends on reduced oxidation of glucose.

The normal consumption of oxygen by the brain is 3.4 cc. per 100 g brain tissue per minute (*Kety et al.*). The corresponding amounts are for the kidney 6 cc., for the heart 8–10 cc.

An increased demand of oxygen in the tissues is satisfied by dilatation of the arterioles, which leads to an accelerated blood flow and so to a higher tension of oxygen in the capillaries. The gradient of oxygen tension from capillaries to the cells is increased, the raising oxidation will cause an augmentation of CO_2—and lactic acid-production, which enhances the dissociation of hemoglobin, the oxygen consumption of the cells reduces their oxygen tension—all factors contribute to a facilitation of oxygen diffusion from capillaries to tissue-cells. At the same time the opening of more capillaries reduces the distance of diffusion from vessel to cell.

These reactions are common to all organs, but certain regulations which are confined to the brain must be emphasized. Conceivably they may play a role for the pathological damages, especially after asphyxia. A constant CO_2-tension in arterial blood seems to be of paramount importance for the maintenance of cell homeostasis. Normally the tension is regulated by respiration through the respiratory centre and the carotid gland, supported by bicarbonate excretion in the kidneys. If this regulation fails and the CO_2-tension in the capillaries is reduced (acapnia), the arterioles of the extremities and the trunk will dilate—more carbon dioxide is delivered to the blood. At the same time, however, brain arterioles will contract and the blood flow diminish. The result is an increased CO_2-tension in the cerebral tissue.

Asphyxia will produce the opposite reactions: cerebral vasodilatation and constriction of arterioles elsewhere in the body. This tends to secure the oxygen supply of the brain.

The cerebral vasoconstriction during acapnia (e.g. during hyperventilation) is counteracted when the oxygen supply to the brain is threatened, for example during hyperventilation in an atmosphere of low oxygen content. The local anoxia will then cause a vasodilatation which dominates the effect of acapnic constriction.

It is conceivable that these antagonist vasomotor reactions during different acapnic conditions and the violent dilatation during asphyxia, where at the same time the general blood pressure is raised, are important in determining the pathological changes during certain forms of what is generally listed under the term of cerebral anoxia. In other words, that the damages may not only be interpreted as pure effects of reduced cerebral oxidation.

Space does not allow a detailed description of the different types of anoxia and the conditions under which they develop. We usually distinguish 4 forms: *Anoxic anoxia,* reduced content of oxygen in the alveoles, *reduced oxygen intake. Anemic anoxia,* reduced oxygen capacity of the blood, *reduced transportation. Stagnant anoxia,* reduced blood flow through the capillaries, which involves a reduction of oxygen tension,—*reduced diffusion. Histiotoxic anoxia,* when the cells cannot utilize the oxygen supplied,—*reduced oxidation.*

All these conditions may occur acutely or develop gradually; they are often combined. Under certain conditions there is a "pure" anoxia, under others a simultaneous rise of the CO_2-content of the blood.

The clinical picture of acute anoxia is well-known. The progress of symptoms corresponds to Hughlings Jackson's "levels" of cerebral functions: The highest cortical level is affected first, then the diencephalon, the mesencephalon, and at last the brain stem. Mental deterioration commences when oxygen saturation is below 30 per cent. oxygen and the tension below 14 mm. These are also the limits when the electroencephalogram is changed from a normal to a low frequency rhythm of high voltage. Unconsciousness occurs at an oxygen consumption of 2 cc./100 g brain tissue.

It is conceivable that the range of susceptibility to anoxia of different cerebral areas is correlated to their varying intensity of metabolism. This conception is supported by both *in vivo* and *in vitro* experiments. Also, the visual and the precentral cortex, which are at first affected, are the most vascularized parts of the brain. Their oxygen demand is presumably the largest and so their sensibility is the oxygen want.

It has been claimed recently that hypoxia during foetal life is responsible for a variety of neurological disorders in infancy and childhood, which were until now ascribed to genetic factors. And it is a well-established fact that anoxia (asphyxia) is a dominating cause of both perinatal death and cerebral palsy. Nevertheless the brain of the new-born is more resistant to lack of oxygen than fully developed brain tissue. The metabolic activity seems to be especially low during the first stages of life, and the arterio-venous difference is 8–9 vol./% as against 6–7 vol./% in adults, which points to a low blood circulation rate. So it must be assumed that both chronic hypoxia during the foetal period and asphyxia during the process of birth must reach rather severe degrees before causing damages.

Now both clinical and pathological findings differ considerably in various conditions which are considered anoxic in origin. We meet e.g. with exclusively extrapyramidal symptoms following acute carbon monoxide poisoning and with brain-stem syndromes without perceptory and mental deficiencies as a result of chocking. Pathologically some cases present a purely cellular degeneration in certain areas, others are combined with or dominated by either diffuse perivascular hemorrhages or single gross hemorrhagic malacias.

What in my opinion, is needed is an attempt to correlate the clinical and the pathological observations to the pathophysiological mechanism which produced the damages, to distinguish between the effect of a long-lasting hypoxia and an acute anoxia, between isolated lack of oxygen and asphyxia and so on, taking into consideration not only the reactions of the different cerebral cell areas to reduced oxygen supply, but also the influence of competing vasomotor responses to hyper- and acapnia and reduced oxygen tension.

CEREBRAL ANOXIA—PATHOLOGICAL ANATOMY

By

Erna Christensen
Copenhagen, Denmark

Cerebral anoxia may occur at any time of life. In recent years, especially, it has been realised how great a rôle birth anoxia plays in primary infant mortality and in the various forms of cerebral palsy (including certain forms of oligophrenia).

Throughout life cerebral anoxia is seen to occur after attempts at suffocation and drowning, and after various kinds of poisoning, the most frequent of which is undoubtedly carbon monoxide poisoning in conne ction with attempts at suicide.

Since the employment of modern methods of anæsthesia, anoxia with fatal outcome or chronic sequelae of anoxia have been observed in conjunction with failure of the oxygen supply owing to a defect in the anæsthetising apparatus. The same appears also after heart stop during the complicated thorax operations.

In all the cases mentioned here we are dealing with universal cerebral anoxia. Sequelae after local cerebral anoxia occur particularly in the older age groups in patients with thromboses or emboli in the larger or smaller cerebral vessels which, on complete blocking, give rise to encephalomalacia. This is also seen after ligation of cerebral arteries to stop hæmorrhage. Small cortical necroses may appear after excessive loss of blood, causing a state of anoxia. Around slowly progressing tumours the blood and oxygen supply may be reduced, and this hypoxia may cause chronic degeneration of both the grey and the white matter, with gliosis, while encephalomalacia may be seen around cerebral hæmatomas and rapidly progressing tumours.

Before we go into the pathologico-anatomical changes resulting from cerebral anoxia, it is important to understand the mechanism of the development of this condition as well as the different types of anoxia (*Courville*).

1. *Stagnant anoxia* in which the blood flow is reduced or suppressed resulting in decrease or lack of oxygen supply to the nerve cells.
2. *Anæmic anoxia.* Here less oxygen is available in the blood stream on account of the smaller amount of hæmoglobin present so that only a small amount of oxygen can reach the nerve tissue.
3. *Hypoxic or anoxic anoxia* occurs, for instance, during anæsthesia if the oxygen supply fails. Consequently, a smaller amount of oxygen will be absorbed in the blood, resulting in a lowered oxygen supply to the brain.
4. *Histiotoxic anoxia* occurs when the nerve-cell membrane is damaged so that the oxygen cannot be absorbed, even though it be present in sufficient amounts.

Cortical encephalomalacia is always present, except in cyanide poisoning where only demyelinisation appears. In cases of nitrous oxide and carbon dioxide anoxia, changes in the grey matter occur in the form of necroses, while in the white matter demyelinisation processes are seen. Peripheral neuropathy appears only after carbon monoxide poisoning.

It is difficult to say with certainty how long the central nervous system may be exposed to anoxia before irreparable processes arise as this depends on several factors:

1. The condition of the patient at the time. Elderly people or anæsthesised patients in a poor general condition are only able to stand a slight reduction of the oxygen supply as compared with other patients before definite histological changes take place in the central nervous system because histologically these patients have a very narrow margin of variation on account of the lowered compensatory possibilities of their arterial system.
2. Susceptibility to anoxia increases with age.
3. The degree and duration of the hypoxia/anoxia are of decisive importance in that sudden exposure to marked hypoxia is far more serious to the patient than repeated exposure to protracted, mild hypoxia (*Morrison*, 1946; *Courville*).
4. The vulnerability of the different parts of the central nervous system is variable. *Morrison* has demonstrated that the ganglion cells in the cortex are particularly sensitive, and that the frontal cortex is the most sensitive while the temporal cortex is the last to be damaged.

The cerebellum is affected before the basal ganglia, and the spinal cord not until the anoxia becomes fatal.

According to *Laughton Hewer,* the order in which the different parts of the central nervous system are affected by anoxia is the reverse of that of their development. Thus, highly specialised areas of the cortex cease to function first, and the vital centres of the medulla oblongata last. If this were not so, the different anæsthetics employed would cause death instead of anæsthesia, as the action of most of them is dependent upon a reduction in the volume per cent of oxygen —and only a few are histiotoxic.

The reason why hypoxia first and most markedly affects the nerve-cells in the cortex seems to be that the oxygen consumption of these cells is greater than that of the various other nerve-cells in the central nervous system. When the oxygen per cent. in the organism is lowered, the cortical cells with the greatest oxygen consumption will be affected first, thus causing unconsciousness, even though for quite a long while there is oxygen enough for the other cells in the brain to function normally. Consequently it might be assumed that reduction of the volume per cent of the oxygen alone would bring about a state of anæsthesia—but in practice it is anoxia that results from this condition, and it is only practicable to obtain a very brief anæsthesia before irreparable changes set in —or even death. With the anæsthetics, however, the degree of anoxia—or rather hypoxia—may be regulated in such a manner that the patient is kept anæsthetised without irreparable nerve-cell changes taking place.

Direct experiments with the oxygen consumption of the different types of nerve-cells are difficult to carry out, and the results of such experiments are uncertain. Animal experiments, however, seem to indicate that, when exposed to anoxia, the different types of cells disintegrate after the following time intervals:

Small pyramidal cells in cerebral cortex	are	destroyed	after	8	min.	anoxia
Purkinje cells in the cerebellum	,,	,,	,,	13	,,	..
Nerve-cells in the medulla oblongata	,,	,,	,,	20–30	,,	..
Nerve-cells in the spinal medulla	,,	,,	,,	45–60	,,	..
Nerve-cells in the sympathetic ganglion	,,	,,	,,	3–3½	hours'	..

Weinberger, Gibbon & Gibbon found that laminæ III–IV in the motor cortex in animals were affected first.

Windle, Becker & Weil have carried out experiments on brain changes in guinea-pigs suffering from birth anoxia. First they found chromophobia in the ganglion cells; after 3 hours there were both swelling and shrinkage of the cells; after 5 hours, poor staining of the cells, and after 2 days chromatolysis. Shrinkage of the ganglion cells was not demonstrated until after 4 days, while hyperchromasia was observed only after the third week. Focal necroses were seen in 8 of the experimental animals.

Erik Krogh has investigated the effect of experimentally produced acute anoxia on the large motor anterior horn cells in the spinal cord in rabbits. Although—as mentioned above—the changes there take place later than in the cortex, the mechanism is the same:

1. *Nissl's acute swelling* with chromophobia and eccentric nucleus.
2. Anoxia of a little longer duration causes *Nissl's severe cell degeneration*. Here the borders of the ganglion cells are blurred; the cells are vacuolised, they stain heterogeneously, and the nuclei cannot be made out.
3. An even more serious injury to the cells is *Spielmeyer*'s *ischæmic cell degeneration*. Here the ganglion cells are shrunken, intensely stained and contain only a few vacuoles and a small dark nucleus.
4. The final stage before the cell disappears entirely is a colourless cell shadow.

In man it is often difficult with absolute certainty to say how long the oxygen deficiency has lasted, and whether the condition is one of hypoxia or anoxia. As different animal species tolerate oxygen deficiency in varying degree, it is not practicable from results of animal experiments to make parallel comparisons with man.

We know that sudden total anoxia in man leads to loss of consciousness within a few seconds, and that irreparable damage to the nerve-cells occurs after 10–13 min.

According to *Courville,* identical conditions are found if we compare the histological changes in man after poisoning with nitrous oxide and other asphyxiating gases with the histological picture after temporary ligation of the vertebral and carotid arteries and after reduction of the oxygen content in the inspired air.

In *Courville*'s opinion, the changes occur as a result of disturbances in the respiratory exchange between the tissue fluids and the cellular elements. It is not only the ganglion cells that degenerate, but also the astrocytes. In contrast to the ganglion cells the astrocytes have a tendency to proliferation in the periphery of the necrotic foci, and in conjunction with proliferating vessels they form a typical astrovascular scar. In the fresh necrotic foci, proliferation of microglia cells are seen, appearing as macrophages.

That operated patients die or get irreparable anoxic changes in the brain in conjunction with the anæsthesia is seldom due directly to the anæsthetics but most frequently to operation shock together with a protracted fall in the blood pressure during the operation. The "hypoxic anoxia" is accompanied by a state of stagnant anoxia due to the hypotension seen especially in patients over 50 years of age in whom cerebral injuries may be anticipated, for instance, on account of arteriosclerosis.

When death occurs in young people under anæsthesia, the changes in the central nervous system are likewise dependent upon the duration of the anoxia and survival time (*Steegmann & O'Brien*).

Irreparable anoxic changes in the central nervous system due to stagnant anoxia brought about by hypotension are also seen in persons who are exposed to low air pressure (e.g. airmen flying at high altitudes) and in persons who have been exposed to protracted and marked chilling (*Schnedorf*, *Murphy*, and *Church & Loeser*).

In recent years the literature has contained a number of publications on deaths due to anoxia in which partly the duration of the anoxia is known, partly the survival time. Here conditions have been observed that correspond on the whole with those found in animal experiments (*Löken, Haymaker & Paulsen* and *Eros & Priestman*).

Hypoglycæmia, as seen in cases of protracted insulin coma among psychiatric patients who have been subjected to insulin therapy, will —if irreparable changes are produced—cause the same histological changes in the brain as in other forms of anoxia. This has been demonstrated in animal experiments by *Lorentzen*, who has also reported the case of a patient who died six weeks after a protracted state of insulin coma and in whom multiple cortical necroses were observed, besides injury to the white matter.

It is only during the past ten years that attention has been drawn to the late sequelae in the central nervous system after paranatal asphyxia where a direct traumatic effect on the brain was out of the question.

That cerebral anoxia also plays an important part in the cause of death in the newborn has been demonstrated, among others, by *Gröntoft*, who finds that repeated attacks of asphyxia injure the blood-brain barrier. Furthermore, histological examinations—in conformity with the observations made by *Courville* —indicate that the primary damage occurs in the capillary endothelium, while degeneration of the cerebral parenchyma and neuroglia is of secondary occurrence. Here we have the explanation of the anatomical fundamental element in the development of the mechanism of the different forms of cerebral palsy and oligophrenia due to anoxia, as children who survive these lesions will have symptoms that vary according to the degree and localisation of the anoxia.

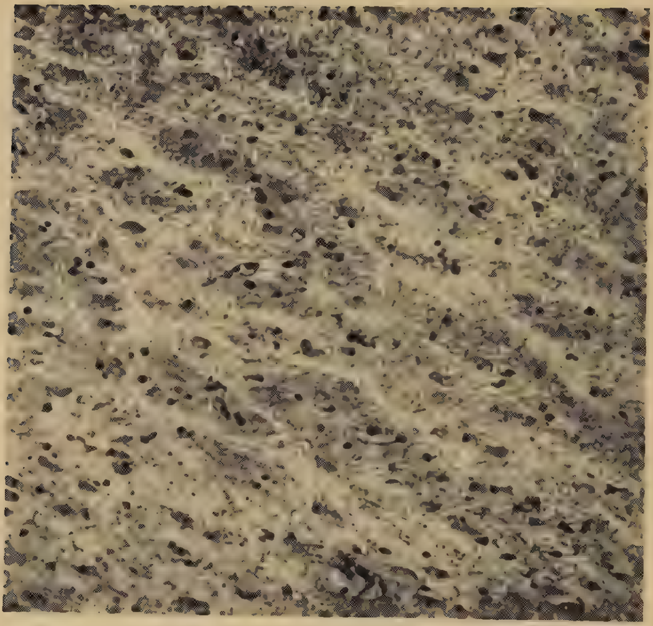
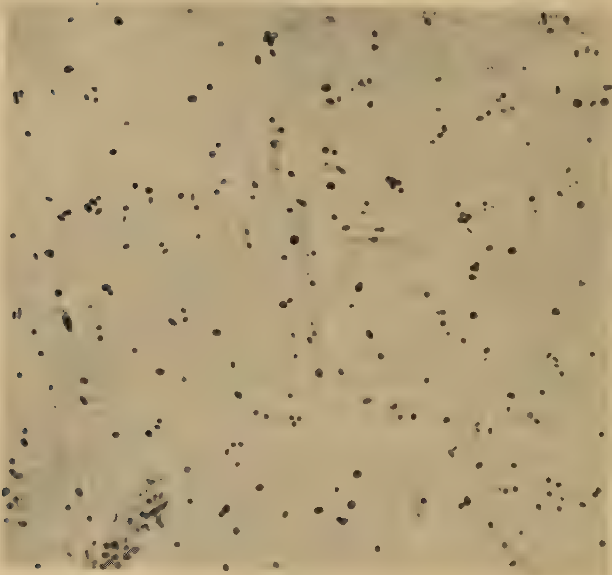


Fig. 1.



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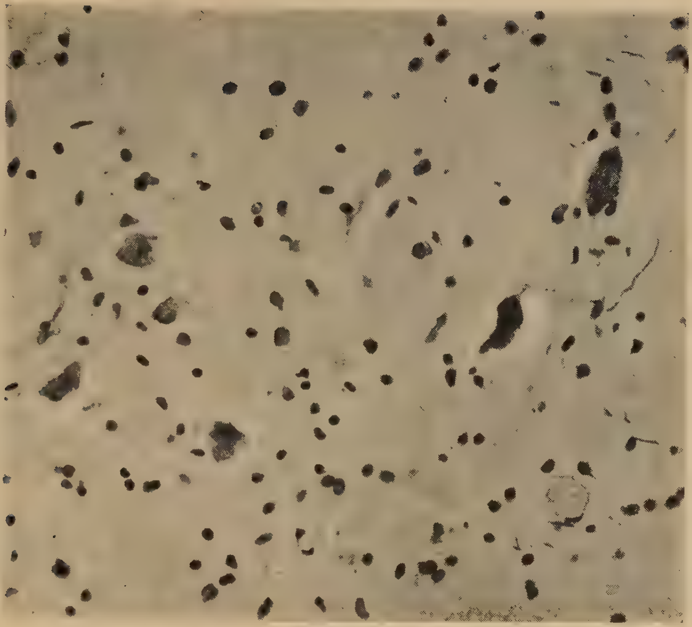

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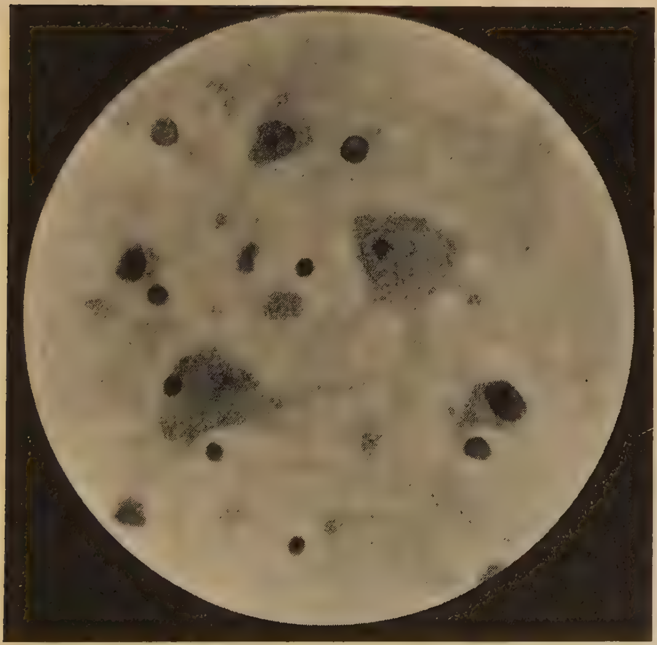

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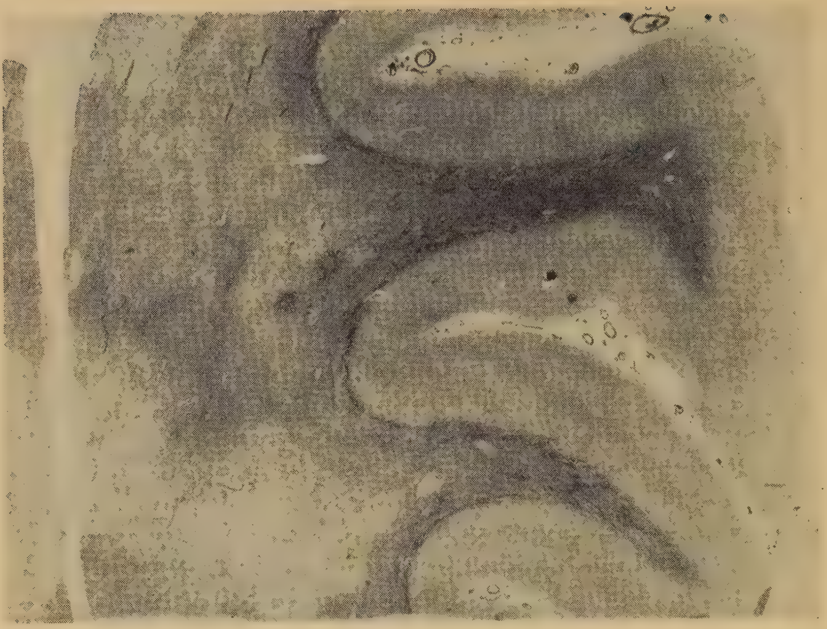

Fig. 5.

According to *Benda,* these anoxia injuries may be divided into the following pathologico-anatomical groups:

1. *Porencephalia,* in which multiple, a single, or a few large cystic cavities are present in the brain in both the grey and the white matter.
2. *Mantle sclerosis,* with slight localised or extensive cortical atrophy.
3. *Disturbances in myelinisation* known as status marmoratus, status dysmyelinatus—mixed extrapyramidal and pyramidal type.
4. *Damage to the medulla oblongata and cerebellum* with consequent cerebellar atactic syndromes.

Courville also calls attention to the fact that in the paranatal anoxias an explanation may undoubtedly be found of many of the degenerative nerve lesions in childhood that previously have not been accounted for, as it is known that anoxia injuries are progressive because of the gliosis which gives rise to secondary progressive damage to the nerve-cells and medullary sheaths.

Paranatal anoxia also plays an important rôle in oligophrenia. Thus, in a survey over the autopsy findings in 88 oligophrenics, *Bredmose* and the writer found positive information about paranatal anoxia in 32.

The views provide for quite a different interpretation of many of the degenerative nerve lesions occurring in childhood, but this aspect can only be touched upon very lightly in the present paper.

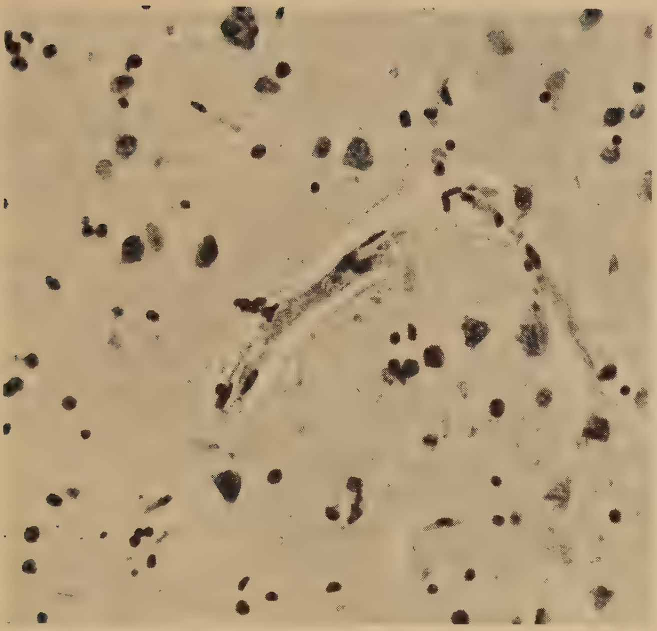

Fig. 6.

After this rather incomplete survey of the literature on the pathologico-anatomical changes in cerebral anoxia, a few illustrations of the different forms of the lesion will be given.

Birth Anoxia—(*Rec. No. Spb. 1506*). Girl, 8 days old, apparently stillborn. Heart action after administration of lobeline and adrenaline. After 8 hours attack of cyanosis and respiratory difficulties with tonic convulsions. At times the child was pale and cold, and it died after 8 days. Histological examination of the grey matter revealed ischæmic ganglion cell changes. *Fig. 1* shows the white matter with degeneration and swelling of astrocytes and oligodendroglia cells.

Anæmic anoxia —after ligation of the common carotid artery. (*Rec. No. Spb. 1503*). Woman, 38 years old, with branchiogenic carcinoma on the left side of the neck. Resection of the left lymph nodes was followed by right hemiparesis. 24 hours later resection of the left common carotid artery was performed with end-to-end anastomosis. The patient died after 24 hours. Fig. 2 shows ganglion cells from the cortex with different degrees of ischæmic degeneration.

Anoxic anoxia. (*Rec. No. Spb. 1400*). Female, 55 years old, in whom anoxia with cyanosis occurred during surgical intervention owing to a defect in the anæsthetising apparatus. In spite of rapid administration of oxygen the respiration and pulse ceased. After 20 min. spontaneous respiration, but the patient remained deeply unconscious, with periodical clonic twitchings in the extremities, and positive Babinski sign until death occurred 19 days after the accident. *Fig. 3* shows ganglion cells degeneration in the nucleus of the dorsal motor nucleus of the n. vagus. Ganglion cell degeneration and vasoparalysis was also seen in the grey matter, and myelin sheath degeneration appeared in the white matter.

Hypoxic anoxia. The following case serves to demonstrate that patients in a poor general condition do not easily stand anæsthetics in rapid succession.

(*Rec. No. Psych. Lab. 051*). Woman, 64 years old, suffering from cancer of the stomach. Gastrectomy was performed in N_2O anæsthesia. The following day the patient had to be reoperated. This time she did not regain consciousness for a long time, and after 4 hours she had a collapse, became somnolent, and died 24 hours after the second intervention. *Fig. 4* shows ganglion cells with swelling and chromatolysis.

Carbon monoxide poisoning. (*Rec. No. Psych. Lab. 0462*). This is a very severe case of accidental carbon monoxide poisoning in which the patient was unconscious for 11 hours before admission to the hospital. The patient became increasingly worse, with falling blood pressure, and died 9 days after the exposure. Histological examination revealed varying degrees of ischæmic ganglion cell degeneration in the cortex. *Fig. 5* shows subcortical necroses.

Allypropymal poisoning (*Histiotoxic anæmia?*) (*Rec. No. Psych. Lab. 0344*). Woman, 38 years old, admitted in a state of unconsciousness 40 hours after intake of unknown dose of allypropymal. The patient died 3 days after admission, during which period she had only been conscious for a short while. *Fig. 6* shows varying degrees of ischæmic ganglion cell degeneration in the cortex, and vasoparalysis.

These few examples emphasize the statements in the literature that the histological changes in the central nervous system in different forms of anoxia are independent of the type of anoxia but dependent upon the degree of the anoxia and the condition of the individual patient at the onset of the lesion.

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CEREBRAL ANOXIA—CLINIC

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SOME ANAESTHESIOLOGICAL VIEWS ON ANOXIA CEREBRI

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In dealing with the subject of anaesthesiological views on anoxia or perhaps, to be more exact, hypoxia cerebri, two lines of thought must be followed. On the one hand, attention must be paid to the effect of the anaesthetic agent itself and to the manner in which it intervenes in the cerebral metabolism and induces anaesthesia, and, on the other hand, to the catastrophic situations arising when, owing to other causes, the brain cells are deprived of their external supply of oxygen. The situation at a hypoglycaemia, when there is insufficient substratum for the existing oxygen to oxidize and, as far as the cell is concerned, the same consequences are involved as in a pure anoxia, lies outside my part of the subject.

As early as 1875 *Claude Bernard* concluded his monograph on the relation between the anaesthetic agent and asphyxia by stating that the former produced its effect on the cerebrum by interfering with oxidation in its cells. Since those days many theories concerning anaesthesia have seen the light, but I shall merely mention the *Meyer-Overton* theory of which the substance's solubility quotionet oil/water forms the central point, that of *Lilles* and *Traubes,* who maintain that the anaesthetic effect is directly dependent on viscosity and surface tension, and that of *Gellhorn,* who described a change in the permeability of the plasmic membrane of the cells during anaesthesia. These theories indicate a possible manner for the anaesthetic agent to get into the cells, but mentions nothing af how its effect is obtained. *Quastel* and *Wheatly* (1) have demonstrated that the anaesthetic agent more easily inhibits oxidation of glucose, lactate, and pyruvic acid than that of glutamic acid and, in addition, that the oxidation of sodium succinate is in no way affected. At what point in the chain of disintegration the effect is exerted has been the subject of lively discussion, but it is now generally held that it is the oxidation of flavoprotein through the cytochrome system which is stopped. In brief, it is the anaesthetic agent that makes oxidation of glucose incomplete, resulting in lowered cerebral respiration, i.e. a form of anoxia is obtained that might perhaps be designated as controlled histotoxic anoxia. It would appear obvious that this histotoxic anoxia is completely reversible, but this has never been definitely proved. It is possible to suppose that each general anaesthetic inflicts a permanent injury on a small number of cells, but that the compensatory margin in the central nervous system is so great that the injury escapes clinical observation. This latter explanation is, however, scarcely credible, the reasons for which I shall return to below (2).

The first phenomenon to occur biochemically in the cell in all forms and at all the early stages of anoxia is the appearance of an intracellular oedema, which can later pursue an extracellular development. Oedematous tissue is difficult to study histologically and this may perhaps furnish an explanation of some of the contradictory reports in the literature. Here much can depend on the fixation process (3).

It is, however, sufficient to say that the theory of *Buzzard* and *Greenfield* (4), which was put forward as early as 1923 and in which it is maintained that the anoxic effect can be cumulative, has been substantiated by animal experiments.

The cumulative effect, however, need not necessarily be caused by the same type of anoxia, any kind of combination being just as dangerous.

This is of great importance for clinical anaesthesia. Prolonged deep narcoses can result in a certain cellular oedema cerebrally, which, nevertheless, disappears if the patient is allowed sufficient time and if no further anoxic traumas attack him. Circulatory difficulties with bleeding and shock or defective ventilation postoperatively can constitute such an additional load that the reversible change becomes irreversible. It must always be remembered that the usual reflectory response on the part of the organism to anoxia in the anaesthetized patient is at least partly out of action. Consequently, we obtain no compensatory increase in cardiac output nor any increase in ventilation.

For the same reason it may be injurious to expose a patient to repeated anaesthetics before a restitution of the cerebrum after the preceding anaesthetic has been obtained and the oedema has been absorbed. As an illustration of what can be achieved with, so to say, simultaneous double anoxic trauma to the cerebrum I shall quote a few figures from some investigations which are being carried out by *Ole Berg* and *Erik Vinnars* (5) at the Neurological Clinic and Department of Anaesthetics here in Lund. During recent years the technique of so-called controlled low blood-pressure during operation has been generally accepted in the different branches of surgery. Low blood-pressure is induced by paralysing the musculature of the vascular walls with a preparation of hexametonium or with arfonad—the latest drug to appear in this field. In other words, the patient is rendered orthostatic and this has been utilized to induce a bloodless field of operation. When the field of operation is situated in the head or in the upper half of the body this involves the head-end of the operating table being raised and the blood-flow being cerebrally reduced and retarded. Thus we have here two anoxic traumas: the anaesthetic itself and, in addition, the reduced circulation.

The patients have been subsequently examined in accordance with Berg's method by evipan tests and their effect on flicker fusion. Of 29 such patients 15 had received hexametonium and 14 arfonad in order to induce hypotension. In the first group a blood-pressure was maintained of between 60–80 mm syst. during a period varying between ½–2¼ hours. Of these 15 patients 6 had a positive evipan test from

2–6 days. Five of these 6 had been lying with a raised head-end, varying between 10–20°. In the arfonad group all patients had been lying horizontally and were under 60 years of age. All were anaesthetized with ether and the pressure was at 70–80 during relatively short periods of ½–1 hour. Also here 6 patients showed a positive test. Yet not one was positive for more than 2 days.

As control, a group of 24 patients with gall-bladder disease, selected at random and of the same age-group, was investigated. The trauma here was therefore only the anaesthetic. In no case could a positive evipan test be induced. Some individual patients were also investigated in whom accidental hypoxic periods from different causes and of varying duration occurred during anaesthesia. All of these showed a positive evipan test. The duration of the positive test, especially in the arfonad group, was short and the injury reasonably small and reversible. Yet in my opinion it may be wise not to use the low-pressure technique to excess nor without absolute and severe indications.

In 1954 *Finck* (6) called attention to an old clinical observation, a kind of anoxia, which is of especial interest in connection with anaesthesia. To the classical division of anoxia into arterial or anoxic anoxia, stagnant anoxia and histotoxic anoxia, he added what he calls diffusion anoxia. This is really a special form of arterial anoxia and is based on the following.

During a nitrous oxide anaesthesia of moderate or considerable length a certain quantity of gas collects in the body, calculated to be about 25–30 litres in volume. When the anaesthesia is finished and the patient is permitted to breathe atmospheric air, this quantity of gas in the body must be removed. Owing to the easy solubility of nitrous oxide in the fluids of the body and its rapid diffusion there occurs during the first few minutes' inspiration of ordinary air a rapid outpour of N_2O into the lungs (Figs. I and II). Up to 12 % has been recorded in the alveolar air. This quantity of gas takes part of the collected partial pressure, mainly at the expense of the O_2 tension. The O_2 saturation of haemoglobin consequently falls and can go down to 85–80 %, and a brief anoxia is present.

In ordinary cases a patient recovers from such a relatively mild and brief anoxia without any injury being sustained. But if a patient has a reduced respiratory parenchyma and a relatively small surface, where the diffusion occurs, as e.g. after a lung extirpation, a very serious hypoxic period can arise. If a patient does not have an entirely satisfactory circulatory status, as in e.g. a coronary insufficiency, the myocardium can perhaps be kept relatively well oxygenated during anaesthesia and surgical intervention, but the short period of diffusion

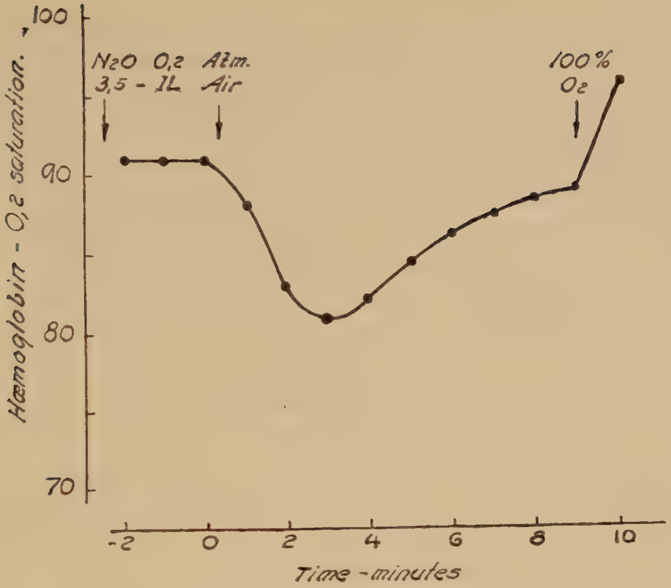

Fig. 1.

Arterial oxygen saturation on waking from N_2O anæsthesia.

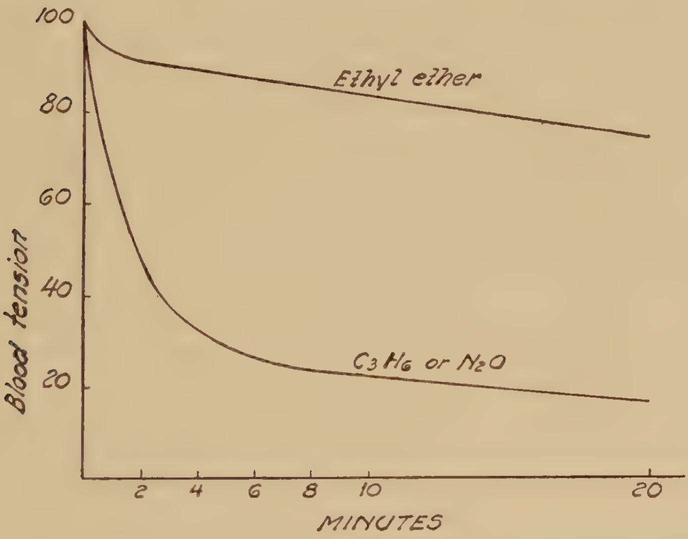

Fig. 2.

Elimination curve for anæsthestic agents. (After S. S. Kety).

anoxia suffices to give insufficiency symptoms, in the first place from the heart and, as a result of this, perhaps cerebral injuries.

Great care is therefore absolutely necessary after prolonged anaesthesias with nitrous oxide and especially when dealing with patients in the advanced risk classes in a respiratory and circulatory respect. A patient of this kind must not be transferred to atmospheric air directly the anaesthesia is interrupted, but this must proceed slowly and via pure O_2 inhalation. The same risk as at the close of the anaesthesia is of course present every time the latter is interrupted during operation for some reason or other, e.g. sucking out the airways.

Another catastrophic situation in connection with anaesthesia will be dealt with here, viz. cardiac arrest. It is of course impossible to give any accurate information as to how often this condition can arise, but the average of 30 American hospitals as given in a survey by *Stephenson*, 1953, is about 1/2500 anaesthesias (7). In a survey from Massachusetts General Hospital, Boston, 1954, a figure of one cardiac arrest in about 1500 anaesthesias was reported. Any idea of the size of the figures in Sweden cannot be obtained as no records of these cases exist. But if the American figures have any counterpart at all in Sweden, it would be a mater of one or two hundred annually.

In cardiac arrest during operation the brain is exposed to three kinds of anoxia. Stagnant anoxia, because the circulation stops; histotoxic anoxia, on account of simultaneous anaesthesia; and a hypoglycaemia locally, because there is no reserve of carbohydrates. It is not possible to state with accuracy how long the cerebrum can be deprived of oxygen and then resume its normal function. In animal tests *Kobot* and associates give the time for a non-anaesthetized dog as 8 minutes. For an anaesthetized person the time is certainly considerably lower, and 3–4 minutes must be taken as the hypothetical working maximum during operation. The ability to withstand anoxia is moreover directly associated with age, and old patients are therefore considerably more vulnerable on this point than young ones.

In the treatment of cardiac arrest during anaesthesia it is above all necessary to induce a circulation of sufficiently oxygenated blood through the cerebrum. The time factor overshadows everything else, and time must not be wasted in unnecessary physical examination. To induce circulation through the cerebrum, on the one hand, artificial respiration with pure oxygen must be started immediately, and, on the other, cardiac massage must be initiated so that blood can be pumped out into the body. Massage is most suitably performed by thoracotomy on the left side. It is important to know whether the cardiac massage is effective, i.e. whether the cerebrum by this means obtains a circulation entailing a certain supply of oxygen. Before the massage is begun the pupils are dilated on account of severe anoxia. If they contract owing to the massage, this may be taken as proof that the oxygen is being supplied to the brain and consequently that the procedure is taking effect. Should the pupils dilate maximally again, the efforts to rescue the patient may be broken off.

Discussion has taken place as to the part played by adrenaline in treatment intended to restore normal cardiac activity. It is, however, certain that in order to recover a normal rhythm, two things are necessary, (1) a satisfactory oxygenation of the myocardium, and (2) a good tonus of the cardiac muscles. A good tonus can be induced by a small dose of adrenaline, 0.2–0.5 mg intracardially. Alternatively, the heart can start to fibrillate in connection with adrenaline treatment, and it is therefore to be recommended, especially in an operation department for advanced surgery, that an electric defibrillator should be at hand. By means of electric shocks of about 1.5 amps in strength and 0.2–0.5 seconds in duration a fibrillation can be stopped, and by massage the heart activity might change to sinus rhythm. It is possible for the heart to go directly from fibrillation to sinus rhythm in connection with electric shocks of this kind.

When the heart has been resuscitated the question is always how long the cerebrum has been deprived of oxygen? How serious the injury inflicted? What can be done to reduce residual symptoms from the circulation? After each cardiac arrest, however, one may perhaps rapidly get the pump mechanism working again, as it must be assumed that the patient has a fairly pronounced post-anoxic cerebral oedema. Unless this oedema is removed as quickly as possible, it is reasonable to suppose that a large number of cells will succumb in spite of the circulation having come into action again. A dehydration therapy should therefore be immediately initiated and maintained during the first 24 hours, and for this human albumin or a 50 per cent. glucose solution should be employed. A too rapid dehydration, however, can induce general spasm. Theoretically, attempts should also be made to increase the circulation through the cerebrum, especially as it is assumed that a certain arterial spasm is often present. Stellate ganglion blocks have been suggested.

Is there, therefore, any manner of making the brain more resistant to anoxia? We know that the foetus and the new-born are better equipped in this respect than the adult (8). This can of course be partly explained by the haemoglobin of the foetus possessing another dissociation curve, and partly by its brain having a larger supply of glycogen, which can be disintegrated and metabolized anaerobically. If any method of stimulating the brain of the adult to completely anaerobic respiration could be produced, it would be of the greatest value in catastrophic situations.

Another interesting thing is that the suprarenal cortex of the foetus and the new-born is far greater than that of the adult, which is levelled out after the first six months of life. Children with cyanotic congenital heart diseasê retain their suprarenal cortex, thus also retaining their increased resistance to anoxia. It has also been possible to produce an increased tolerance to anoxia by applying cyphochrome C.

If we turn to comparative physiology we find that diving mammals possess a peculiar faculty. A seal, for instance, can stay under water for a long period and surface with a haemoglobin saturation—according to *Krogh*—of very nearly zero but with consciousness retained (9). In the explanation of this phenomenon there may perhaps lie something of inestimable value to all clinicians.

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CEREBRAL ANOXIA—FLICKER FUSION

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KOHLENOXYDVERGIFTUNG

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Kohlenoxyd ist von besonderem Interesse in dem hier behandelten Thema auf Grund seiner spezifischen Affinität zum Haemoglobin, mit dem es sich principiell auf gleiche Weise wie Sauerstoff, jedoch mit

einer ca. 245 mal grösseren Intensität als dieser, verbindet. Das ist die einzige, mit Sicherheit festgestellte Wirkung des Kohlenoxydes auf den Säugetierorganismus. Im übrigen ist es ein indifferentes Gas von derselben Art wie z. B. Stickstoff. Genau wie Stickstoff löst es sich in den Gewebsflüssigkeiten, scheint sich aber nicht noch anderweitig als durch Blockade von Haemoglobin an biologischen Reaktionen zu beteiligen. Jedoch gehen die Meinungen in dieser Frage auseinander. In der sehr umfangreichen Literatur über Kohlenoxyd brachten eine Reihe von tierexperimentellen und klinischen Untersuchungen Ergebnisse, die zu Gunsten der Auffassung gedenkt werden können, dass das Kohlenoxyd den Säugetierorganismus auch noch auf andere Weise als nur durch Störung der Eigenschaft des Haemoglobines, Sauerstoff zu binden, beeinflusst. Versuche in vitro haben erwiesen, dass das Kohlenoxyd unter bestimmten Voraussetzungen gewisse Fermente, z. B. Warburgs Atmungsferment, beeinflusst. Einige klinische Beobachter haben Symptome festgestellt, in welchen sie ein besonderes Syndrom wahrgenommen haben wollen, dessen Aethiologie Kohlenoxyd ist, das während einer langen Zeit dem Organismus in so kleinen Mengen zugeführt wurde, dass manifeste, akute Hypoxiesymptome nicht erwarten waren. Der in Frage kommende Krankheitsbegriff ist von Klinikern, die der Frage ein kritisches Studium widmeten, nicht allgemein anerkannt worden.

Eingangs einige Worte über das häufigste Vorkommen von Kohlenoxyd und die wichtigsten Ursachen akuter Vergiftungen.

Kohlenoxyd kommt in gewöhnlichen Leuchtgas zu 8 20 % und in Auspuffgasen von Bensin-Verbrennungsmotoren zu 1–10 % vor. Ein paar Beispiele über Ursachen zu Kohlenoxydvergiftungen sind ausströmendes Leuchtgas, Leerlauf von Automotoren in Garagen und Kohlenoxydentwicklung bei Feuersbrünsten.

Das Kohlenoxyd erreicht und verlässt den Organismus praktisch nur durch die Lungen. Es ist wasserlöslich, durchdringt die Wasserphase des Lungenendothels und der Kapillarenwände und gelangt auf diese Weise zum Haemoglobin. Hat das Kohlenoxyd das Blut erreicht, konkurriert es mit dem Sauerstoff, den es auf Grund seiner hohen Affinität zum Haemoglobin verdrängt. Da der Partialdruck des Sauerstoffes in der Alveolarluft 100 mm Hg beträgt, ist ein Kohlenoxydpartialdruck von weniger als einem halben mm Hg ausreichend, um das Haemoglobin zu 50 % mit Kohlenoxyd zu sättigen. Daraus folgt, dass man bei der Herstellung von Blut mit 50 % Kohlenoxydhaemoglobin, dieses einer Atmosphäre, die ca. 14 % Sauerstoff aber nur ungefär 0,06 % Kohlenoxyd enthält, aussetzt. Die Kohlenoxydkonzentrationen in Luft, die erforderlich sind, um einen beträchtlichen Teil des Haemoglobines zu blockieren, sind demzufolge erstaunlich gering. Zufolge der geringen Gehalte dauert es jedoch eine verhältnismässig geraume Zeit, ehe sich das Gleichgewicht bei einem bestimmten Sättigungswert einspielt, d. h. ehe dem Blut die erforderliche Kohlenoxydquantität zugeführt ist. Da sich Kohlenoxyd in demselben quantitativen Verhältnis wie Sauerstoff an Haemoglobin bindet, enthält Blut bei einem Kohlenoxydhaemoglobinwert von 50 % und bei einer Gesamtblutmenge von 5 Litern ca. 0,5 Liter reines Kohlenoxyd.

Vol. % CO in Luft (21% O_2)	HbCO % in Blut											
	bei Ventilation von 6 Liter (Bettruhe) bzw. 10 Liter (leichte Bewegung) und 20 Liter (leichte Arbeit) Pro Min. nach verschiedenen Zeiten (Min.) (Berechnungen nach HATCH, 1952)											bei Gleichgewicht zwischen CO in Luft und Blut
	50	100	150	200	300	400	500	600	700	800	1200	
0,01	1,5	2,9	4,2	5,5	7,3	8,8	9,9	10,8	11,5	12,0	13,3	14,0
	2,5	4,6	6,3	7,7	9,8	11,2	12,2	12,7	13,2			
	3,9	7,0	9,0	10,5	12,4	13,1						
0,02	3,0	5,7	8,4	10,3	14,0	16,5	18,5	19,9	21,2	22,1		24,6
	4,9	9,1	12,3	14,8	18,5	20,7	22,1	23,1				
	7,8	13,3	17,0	19,4	22,1							
0,04	5,9	11,4	15,8	19,7	25,6	29,5	32,7	34,7	36,2	37,0		39,4
	9,5	16,9	22,5	26,8	32,3	35,3	37,1					
	15,0	24,0	29,9	33,5	37,2							
0,06	8,9	16,8	22,7	27,7	35,1	40,0	43,2	45,5				49,4
	14,3	24,2	31,1	36,6	42,9	46,0						
	21,2	33,6	40,5	44,5								
0,08	12,4	21,5	29,4	35,0	43,5	48,6	51,5	53,7				56,5
	18,6	31,1	39,0	44,6	51,1							
	28,3	42,4	49,2	52,8								
0,10	14,9	26,0	34,7	40,9	49,6	55,2	57,9					62,0
	22,3	36,0	45,8	51,5	57,7							
	32,9	48,4	55,2	58,9								

Exponiert man ein Individuum kontinuierlich in einer Atmosphäre, die einen konstanten Kohlenoxydgehalt enthält, erreicht man früher oder später ein Gleichgewicht zwischen dem Kohlenoxyd der Atmungsluft und des Haemoglobines.

Die zur Einstellung des Gleichgewichtes erforderliche Zeit ist hauptsächlich von der Lungenventilation abhängig. Je intensiver die Ventilation ist, desto schneller erreicht das Kohlenoxydhaemoglobin den Sättigungswert, welcher der Kohlenoxydkonzentration der Luft entspricht (siehe Tabelle).

Exponiert man z. B. eine ruhende Person in einer Atmosphäre, die 0,08 Vol.-% Kohlenoxyd enthält, erhält man allmählich einen Kohlenoxydhaemoglobinwert von 55 %. 90 % dieses Wertes, d. h. 50 % erhält man bei einer Ventilation von

6 Liter/min. nach 8 Std.
8 Liter/min. nach 6 Std.
10 Liter/min. nach 4½ Std.

Das Verhältnis der Zeit zu verschiedenen Kohlenoxydgehalten, die unter gleichartigen Bedingungen gleiche Kohlenoxydhaemoglobinwerte geben, wird im Folgenden erklärt: Bei einer Lungenventilation von 6 Liter/Min. erhält man einen Wert von 30 % COHb nach ca. zweistündiger Exposition in einer Atmosphäre, die 0,1 % Kohlenoxyd enthält, aber schon nach ca. 10 Min., wenn die Atmosphäre 1 % Kohlenoxyd enthält.

Alle jene Werte für das Gleichgewicht zwischen Kohlenoxyd der Atmosphäre und des Haemoglobines gelten für Luft, d. h. für eine Gasmischung, die 21 % Sauerstoff enthält. Bei höheren Sauerstoffgehalten ist eine gegebene Kohlenoxydkonzentration vom Gesichtspunkt der Vergiftung aus betrachtet weniger riskant als bei niedrigeren Sauerstoffgehalten.

Die Ausscheidung von Kohlenoxyd erfolgt nach den gleichen Prinzipen wie die Aufnahme. Bringt man ein kohlenoxydvergiftetes Individuum in kohlenoxydfreie Atmosphäre, wird das Gleichgewicht gestört, und das Kohlenoxyd verlässt das Blut durch die Lungen. Der Kohlenoxydgehalt in der Alveolarluft steht mit dem des Blutes im Gleichgewicht, weshalb man in dieser Phase einen vom praktischen Standpunkt aus Gesehen adäquaten Ausdruck für den Kohlenoxydhaemoglobingehalt erhält, wenn man den Kohlenoxydgehalt der Alveolarluft bestimmt.

Die Geschwindigkeit der Ausscheidung ist wie die der Aufnahme von der Intensität der Lungenventilation und vom Sauerstoffgehalt der Einatmungsluft abhängig. Atmet ein in Ruhe befindliches Individuum mit 50 % Kohlenoxydhaemoglobin in kohlenoxydfreier Atmosphäre erreicht der COHb-Wert nach 4½ Std. die Hälfte, d. h. 25 %, und nach 14½ Std. ein Zehntel, d. h. 5 %. Bei leichter körperlicher Bewegung, die u. a. intensivere Lungenventilation veranlasst, sinkt der COHb-Wert schon nach 2½ Std. auf 25 % und nach 8½ Std. auf 5 %, d. h. im grossen und ganzen doppelt so schnell.

Die Blockade von Haemoglobin durch Kohlenoxyd veranlasst eine verminderte Sauerstoffkapazität im arteriellen Blut. Exponiert man ein Individuum bis zu einem Kohlenoxydhaemoglobinwert von 50 %, befindet es sich vom Standpunkt der Sauerstofftransportmöglichkeiten gesehen in derselben Lage wie ein Individuum mit einer 50-%igen Anaemie. Es ist schwierig einen exakten Vergleich zwischen dem klinischen Bild einer Kohlenoxydvergiftung und einer *akuten* Anaemie mit anderer Ursache, z. B. Blutung oder Haemolyse, anzustellen und daraus Schlüsse zu ziehen. Der zeitliche Verlauf, Gefässreaktionen und lokalisierte Organschäden stören den Vergleich zu sehr. Trotz dass die Gewebe bei einer chronischen Anaemie anderweitige Möglichkeiten zur Adaption als bei einer akuten Haemoglobinblockade haben, gestaltet sich der Vergleich zwischen diesen weniger schwerfällig. Ein Mensch mit einer Anaemie mit 40 % Hb ist im allgemeinen in der Ruhe subjektiv ohne Beschwerden. Erst bei physischen Anstrengungen machen sich Dyspnoe und andere Beschwerden bemerkbar. Ein kohlenoxydvergifteter Mensch mit einem Kohlenoxydhaemoglobingehalt von 60 % – der demzufolge auch 40 % seines Haemoglobines für den Sauerstofftransport zur Verfügung hat – ist in einer ganz anderen Lage. Er befindet sich in tiefer Bewusstlosigkeit und hat oft ernste Kreislauf- und Atmungsinsuffizienz. Dieser Vergleich zeigt, dass der Sauerstoffbedarf der Gewebe – wenn man annimmt, dass dieser in beiden Fällen gleich ist – bei 40 % Hb + 60 % COHb schlechter als bei nur 40 % Hb befriedigt wird. Der Unterschied ist physiologisch damit zu erklären, dass Kohlenoxydhaemoglobin die Sauerstoffbindungskurve des unveränderten Haemoglobines nach links, d. h. in die entgegengesetzte Richtung wie Kohlensäure, verschiebt. Während das Kohlendioxyd die Dissoziation des Oxyhaemoglobines erleichtert, erschwert das Kohlenoxyd diese und hemmt damit die Sauerstoffabgabe an die Gewebe. Dadurch muss sich der Sauerstoffdruck in den Geweben auf einen niedrigeren Niveau halten, um durch das grössere Spannungsgefälle dieselbe Sauerstoffmenge wie bei Vorhandensein von nur Oxyhaemoglobin zu erlangen. Das kann man am niedrigeren Sauerstoffdruck im Venenblut ablesen. Eine Verminderung des *totalen* Sauerstoffverbrauches des Individuums soll bei Vergiftungen bis zu 50 % COHb nicht vorliegen.

Will man den Zustand eines kohlenoxydvergifteten Individuums mit dem eines solchen vergleichen, dessen Sauerstoffgehalt im Blut durch Respiration von Luft mit niedrigem Sauerstoffdruck äquivalent vermindert ist, muss auf einen wichtigen Unterschied Rücksicht genommen werden. Bei Kohlenoxydvergiftungen ist der Sauerstoffdruck des arteriellen Blutes normal, d.h. 100 mm Hg, da dieser ganz und gar vom Sauerstoffgehalt in der Alveolarluft, der ca. 14 % beträgt, bestimmt wird. Bei verminderter Sauerstoffgehalt des Blutes durch Senkung des Partialdruckes des Sauerstoffes in der Alveolarluft bei z.B. Atmung von Luft mit geringem Sauerstoffgehalt, ist der Sauerstoffdruck des arteriellen Blutes in gleichem Masse vermindert. Wenn das Blut mit dem niedrigen Sauerstoffdruck wie im letzteren Falle das Kontrollorgan, das Glomus caroticum, durchströmt, wird dieses adäquat gereizt und löst Kompensationmechanismen, u.a. gesteigerte Lungenventilation, aus. Bei gleicher Herabsetzung der Sauerstoffkapazität des Blutes durch Kohlenoxyd, findet ein solcher Einfluss auf das Glomus caroticum nicht statt, da ja die Sauerstoffspannung normal ist.

Einer verminderten Sauerstoffversorgung der Gewebe begegnet das Kreislaufsystem mit Dilatation der peripheren Gefässe und Eröffnung neuer Kapillaren. Dadurch werden Voraussetzungen für eine kompensatorisch gesteigerte Durchblutung geschaffen. Die Eröffnung neuer Kapillaren bedingt eine Verkleinerung des Abstandes zwischen den Blutkörperchen und den Gewebszellen, wodurch der Diffusionsweg des Sauerstoffes verkürzt wird. Bei Kohlenoxydhypoxie scheinen diese Reaktionen der peripheren Gefässe wesentlich markanter als bei anderen Hypoxieformen zu sein. Nach Sjöstrand (1935) ist Kohlenoxyd einer der stärksten uns bekannten gefässdilatierenden Faktoren. Aber wahrscheinlich ist die Gefässdilatation nicht Ausdruck eines spezifischen Kohlenoxydeffektes, sondern leitet sich nur von der Hypoxie ab. Während die durch geringen Sauerstoffdruck in der Alveolarluft bedingte Hypoxaemie in erster Linie und in einem verhältnismässig frühen Stadium zentral gesteuerte Kompensationsmechanismen auslöst, muss die Kohlenoxydhypoxie vor allem durch periphere Vasodilatation und gesteigerte Durchblutung kompensiert werden. Klinisch bestätigte man diese Reaktion auf Kohlenoxyd durch Beobachtung von Retinalgefässen. Sjöstrand untersuchte die Reaktion des Schädelinhaltes bei akuter Kohlenoxydvergiftung an der narkotisierten Katze. Er fand Dilatation der Piagefässe, Erhöhung des intrakranialen Druckes und Vergrösserung des Hirnvolumens.

SYMPTOMATOLOGIE

Die akute Kohlenoxydvergiftung tritt in zwei Formen, der massiven und der progressiven Form, auf. Der Unterschied besteht nur in der Intensität der Exposition.

Die massive Kohlenoxydvergiftung hat wenig klinisches Interesse. Sie tritt bei Expositionen mit hochkonzentriertem Kohlenoxyd ein und führt schnell zum Tode. Bei Einatmung von reinem Kohlenoxyd sind schon ein oder zwei Atemzüge tödlich. Einatmung von 25–35 %-igem Generatorgas oder 8–20 %-igem Leuchtgas führen in Minutenschnelle zur tödlichen COHb-Konzentration. 0,5–1 % Kohlenoxyd in der Luft führt innerhalb von 5 25 Min. zur tödlichen COHb-Konzentration (75-

%ige Sättigung). Das Charakteristische an diesen auf jene Weise verunglückten Personen ist die hellrote Hautfarbe und die schnell einsetzende Leichenstarre.

Dagegen ist die akute Vergiftung in ihrer progressiven Form von klinischem Interesse. Die Beschwerde bereitenden Symptome leiten sich hauptsächlich vom Nervensystem ab. Die gewöhnlich auftretenden und typischen Symptome bei Kohlenoxydvergiftungen bis zu 50 % Kohlenoxydhaemoglobin sind Kopfschmerzen (besonders Stirnkopfschmerzen), Schwindel, Uebelsein (evtl. mit Erbrechen) und Benommenheit. Herzklopfen ist nicht ungewöhnlich. Manchmal treten auch andere Symptome auf: Agitation, unsicherer Gang wie bei Betrunkenheit, Wutanfall, intensive Wärme- oder Kältegefühle, Sehbeschwerden in Form von Schleiersehen und Gehörstörungen in Form von summenden oder rauschenden Geräuschen.

Das Auftreten und die Intensität dieser Symptome sind von vielen Faktoren abhängig. Erzielt man eine bestimmte Sättigung durch verhältnismässig langdauernde Exposition mit geringen Kohlenoxydgehalten in der Luft, sind die Symptome im allgemeinen ernster als bei schnellerem Erreichen der Sättigung auf Grund eines höheren Kohlenoxydgehaltes. Muskelarbeit spielt eine grosse Rolle. Sie vergrössert den Sauerstoffbedarf und damit die Ventilation, die wiederum die Schnelligkeit, mit der ein bestimmter Kohlenoxydhaemoglobinwert erzielt wird, erhöht. Die Muskelarbeit stellt ausserdem grössere Anforderungen an den reduzierten Sauerstofftransportapparat und ruft dadurch Anoxiesymptome hervor bzw. vergrössert deren Intensität.

Es liegen auch grosse individuelle Variationen in der Reaktion auf Kohlenoxyd vor. Einzelne Individuen können 40 % COHb ohne subjektiven Beschwerden vertragen, während andere schon bei 15–20 % Symptome bekommen.

Bei kurzdauernden Expositionen mit hohen Gehalten treten die Kopfschmerzen in ihrer schweren Form erst nach einigen Stunden nach der Exposition auf, wenn das Kohlenoxydhaemoglobin durch Entlüftung schon auf ungefähr die Hälfte des Anfangswertes gesunken ist. Strengt sich das Individuum dagegen an, können die Kopfschmerzen schon früher auftreten und nicht selten variieren sie da mit dem Grad der Anstrengung.

Bei einer starken Kohlenoxydexposition geschieht es nicht selten, dass eine in Ruhe oder in leichter Arbeit befindliche Person plötzlich schwache Symptome: leichte Kopfschmerzen, leichten Schwindel oder ein leichtes Uebelbefinden bemerkt. Sie vermutet Kohlenoxydeinwirkung und trifft Anstalten, die Lokalität zu verlassen. Die dabei oft nur geringe erforderliche Anstrengung hat zur Folge, dass der Sauerstoffbedarf des Gehirns nicht zufriedengestellt werden kann. Sie verliert das Bewusstsein und fällt schon nach ein paar Schritten zu Boden. Manchmal erreicht sie eine Tür oder ein Fenster, ist da jedoch schon zu benommen oder unsicher mit den Händen, um die Türklinke zu ergreifen oder den Fensterverschluss zu öffnen. Sie bemüht sich noch mehr, verliert das Bewusstsein und stürtzt hin. Es geschieht nicht selten, dass Menschen unter solchen Umständen schwer vergiftet oder tot bei unverschlossenen Türen angetroffen werden.

FOLGEERSCHEINUNGEN NACH AKUTER KOHLENOXYDVERGIFTUNG

Akute Kohlenoxydvergiftungen, die mit einer mehrere Stunden lang dauernden Bewusstlosigkeit ablaufen, können ischaemische Gehirnschäden hervorrufen, die kürzere oder längere Zeit bestehende, evtl. endgültige Symptome geben. Diese Schäden können jeden beliebigen Teil des Gehirns betreffen, befallen aber in erster Linie den Cortex und die Basalganglien. Symmetrische Pallidum-Malazien machen den klassischen pathologisch-anatomischen Befund dieser Fälle aus.

Die Symptome des ischaemischen Gehirnschadens kommen entweder unmittelbar nach der Intoxikation oder erst nach einer Zwischenzeit von einigen Wochen. Während dieser Zwischenzeit konnten die Patienten oftmals gesundgeschrieben werden und die Arbeit wieder aufnehmen. Die Symptombilder sind von teils psychiatrischer und teils neurologischer Art. Die psychischen Symptome können die einer akuten Psychose oder einer bleibenden Dementia sein. Die neurologischen Symptome zeigen typische Fälle mit extrapyramidalen Erscheinungen; im allgemeinen ein Parkinsonbild mit Schwerpunkt auf der Akinese und Rigidität, jedoch ohne oder mit nur geringem Tremor. Auch Hemiplegien, Hemianopsien und Aphasien kommen vor. Sichere kohlenoxydbedingte Rückenmarksschäden sind nicht beschrieben. Soweit kohlenoxydbedingte Polyneuriten auftreten, sind sie sehr selten. Mononeuriten nach Kohlenoxydvergiftungen kommen vor, sind aber wahrscheinlich durch Druckschäden während der Bewusstlosigkeit bedingt.

BEHANDLUNG

Bei der Behandlung müssen zwei Prinzipe massgebend sein:

1) Der Vergiftete darf vor der Auslüftung des Kohlenoxydes seinen Sauerstoffbedarf nicht unnötig vergrössern. Deshalb Verordnung von Bettruhe.

2) Das Kohlenoxyd muss so schnell wie möglich aus dem Blut ent-

fernt werden. Gemäss der eingangs erwähnten Daten über das Verhalten des Kohlenoxydhaemoglobines bei hohem Sauerstoffdruck in der Alveolarluft und damit auch im arteriellen Blut, soll der Patient mit Sauerstoff behandelt werden. Da Kohlendioxyd die Dissoziationskurve des Kohlenoxydhaemoglobines so verschiebt, dass die Abgabe von Kohlenoxyd erleichtert wird, und da es ausserdem die Lungenventilation vergrössert und damit die Entlüftung unterstützt, soll auch Kohlendioxyd zugeführt werden. Der Patient soll also Karbogen (7 % CO_2 in O_2) erhalten.

FOETAL ANOXIA

By

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With the decreasing frequency of traumatical cerebral birth injuries and the recent advances made in the management of the premature infants foetal anoxia appears more and more as an important factor in the causation of perinatal mortality and cerebral palsy. In a number of papers *Courville* (1953) has emphasized the role of anoxia for the development of cerebral complications. However, no conclusive evidence of a causal relationship between foetal anoxia and cerebral palsy has as yet been established but some extensive follow-up studies are in progress i.e. *MacKinney et al.* (1955). Most obstetricians in Sweden accept the view that foetal anoxia not infrequently leads to cerebral haemorrhage during delivery and/or to a later impaired neurological status.

During the last few years we have studied the oxygen saturation in the umbilical cord of newborn infants. The material consisted of specimens collected in association with spontaneous deliveries, caesarian sections, forceps deliveries and of samples collected at the delivery of asphyxiated infants. The results are summarized in Table 1. The arterial oxygen saturation of adults is 96 per cent, while the venous oxygen saturation varies with the degree of physical exertion and usually lies between 40 and 80 per cent. In contrast to the high oxygen saturation of the blood of the mother the blood in the umbilical artery of the newborn infant contains only about 30 per cent oxygen and the vein 60 per cent oxygen. There has been some discussion as to whether the oxygen saturation, as measured in the cord blood immediately after delivery, is the same as in utero during the last few weeks of gestation. *Haselhorst & Stromberger* (1932) maintain that during delivery the oxygen saturation in the umbilical cord increases as a result of the uterine contractions. As we have observed about the same oxygen saturation in infants delivered by caesarian section performed under local anaesthesia as in infants delivered spontaneously, we are inclined to believe that the oxygen saturation recorded was the same as that in utero. A similar observation has been reported by *Watts et al.* (1951) and by *Walker* (1954). In their materials the mothers were under spinal anaesthesia for caesarian section.

In their discussion of the foetal oxygen content *Barcroft* (1946) and later *Eastman* (1954) used the dramatical expression "Mount Everest in Utero". If blood were equilibrated at 10,000 meters it would have the same oxygen content as the umbilical vein of the cord at normal delivery.

This can also be exemplified by determining the percentage of oxygen inspired air must have for the oxygen tension in the cerebral arteries to be the same as in utero. In an adult inhaling 9 per cent oxygen in nitrogen this tension would probably be 28 mm. Hg.

The arteries of the brain of the foetus never have such a relatively high oxygen tension as the umbilical cord, but their oxygen tension is higher than that of the other arteries of the body. This, though known before, has recently been illustrated by *Lind & Wegelius* (1953) using cinematography, showing how the blood flows from the umbilical vein to the inferior vena cava, to the right atrium, left atrium, left ventricle and aorta without being more than slightly diluted by the extremely oxygen-poor blood from the body. Although this blood of high oxygen content from the aorta may pass directly up through the carotid arteries, their oxygen saturation must be lower than that in the umbilical vein.

The foetus should not be compared with unacclimatised adults but rather with adults living at high altitudes, such as the Indians of the Andes. The Chilean miners who live at an altitude of 5,300 meters and work at 6,000 meters above sea level are more comparable with foetuses as regards oxygen tension. In the arterial blood of these miners *Dill et al.* (1937) found the same oxygen tension as in the cerebral arteries of foetuses. It is known that the average duration of life is shorter at high altitudes. It would be interesting to know the oxygen saturation of the foetuses born at this high altitude and how they can develop in spite of the extremely low oxygen content of their blood.

In the sixteenth century, when the Spaniards founded the Imperial City Potosi in Bolivia at an altitude of 4,000 metres, it was more than

50 years before the first Spanish infant survived, although the Indians reproduced with normal fertility *(Boothby,* 1954).

How the foetuses can live and develop with this low oxygen tension is not properly understood, but some reasons are known. They are adapted to a low oxygen tension by having an increased number of red blood cells, different haemoglobin, a lower blood pH, a more rapid circulation, a distribution of blood to the brain relatively rich in oxygen, low carboanhydrase content, and finally by the power of anaerobic glycolysis. It is known that children have survived the true caesarian section, i.e. section of a dead mother, even when the mother had been dead for 15 to 20 minutes. This anaerobic glycolysis is probably of importance during delivery, especially in breech presentations, prolapses of the umbilical cord and asphyxia. *Enhörning & Westin* (1954) described a case of a 19 cm long foetus which survived more than 3 hours without breathing and without air in the intestines, which indicates the extent of the anaerobic combustion.

So far, only physiological foetal anoxia has been mentioned. In some pathological conditions the oxygen saturation is markedly decreased. In infants delivered by caesarian section of mothers under inhalation anaesthesia (usually cyclopropane; nitrous oxide, and ether) the oxygen saturation is low both in the umbilical vein and in the arteries (Table 1).

TABLE 1

Percentage saturation of cord blood.

	Arteries	No.	Vein	No.
Spontaneous delivery without signs of asphyxia	33	69	61	98
Caesarean section under inhalation anaesthesia	20	20	42	22
Caesarean section under local anaesthesia	24	11	53	11
Forceps delivery because of maternal distress ...	35	6	61	8
Asphyxiated children	16	28	39	34

The importance of this anoxia should not be overestimated, because as a rule it only lasts a short time, but during prolonged difficult labour and perhaps also during abdominal operations for purposes other than obstetrical such anoxia may injure the foetus. The high frequency of abortion after laparotomy of pregnant women is well-known, and possibly this anoxia induced by the operation might explain part of the perinatal deaths after caesarian section.

The importance of anaesthesia as a cause of prenatal and postnatal anoxia has been shown by *Taylor et al.* (1955). When the mothers were sedated with Demerol-scopolamine (100 + 0.4 mgm) the oxygen saturation was on the average 59 per cent, as compared with 75 per cent. in those infants whose mothers had not been sedated. The corresponding figures thirty minutes after delivery were 86 per cent. and 98 per cent. *Taylor et al.* (1951) also showed that although etherisation of the mother has hardly any effect on the oxygen saturation of the infant, the use of cyclopropane will depress it.

We found ether anaesthesia for forceps delivery because of maternal distress not to decrease the oxygen saturation. This also suggest that delivery by low forceps does not enhance the risk of anoxia, an observation in line with the extensive follow-up study of *Wetterdal* (1927).

TABLE 2

Range of saturation in cord blood.

	Percentage saturation 0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Spontaneous delivery without sign of asphyxia									
Number artery	4	11	16	15	14	7	2		
Number vein	–	3	1	2	16	25	26	23	7
Asphyxiated children									
Number artery	13	6	7	–	1	1			
Number vein	4	2	2	6	10	4	3	1	

parent from the range of the oxygen saturation values given in Table 2, that the oxygen content of the arterial blood of children delivered spontaneously varied widely, while that of the asphyxiated children

Clinically asphyxiated children have about the same oxygen saturation in the arteries and in the veins as those delivered by caesarian section of mothers under inhalation anaesthesia (Table 1). It is ap-
had hardly any oxygen at all. The oxygen content of the venous blood of the infants delivered spontaneously varied but slightly though low values were occasionally recorded. The oxygen content of the blood in the umbilical vein of asphyxiated infants was very low, though occasionally normal. This is in agreement with the generally accepted view that asphyxia can be due not only to hypoxia but also to other factors such as brain injury or deformity. In two of our clinically asphyxiated children, who died from brain injury within a couple of days of birth, the oxygen saturation was normal and thereby traumatisation during delivery was suggested as a main factor in producing these brain injuries.

Measurement of the oxygen saturation provides a simple method of analysing our cases of asphyxia. When the umbilical oxygen saturation was above 50 per cent., it was said to be normal; when less than 40 per cent., to indicate hypoxia. Only with the aid of such analyses can the ultimate results of hypoxia be properly judged.

A vasomotor reaction due to changes in oxygen and carbon dioxide tension was first described by *Krogh* (1922), for the cerebral vessels by *Tinel* (1927), and for the retinal vessels by *Cobb & Fremont-Smith* (1931). However, at the time of these findings there was no known disease which could be explained by these vasomotor reactions. Studies of retrolental fibroplasia by *Szewczyk* (1952), *Ashton et al.* (1953), and *Huggert* (1952, 1953, 1954) have shown that this disease is caused by too liberal administration of oxygen and that the retinal vessels constrict when the infants are given oxygen.

As children with retrolental fibroplasia often have cerebral palsy or mental defects, it is possible that the same basic mechanism affects both the retinal and the cerebral vessels. It is hoped that investigations based on these assumptions and now in progress will help to elucidate the importance of foetal anoxia.

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THE CEREBRAL OXYGEN CONSUMPTION IN NORMAL HUMANS DETERMINED BY USE OF RADIOACTIVE KRYPTON 85

By

N. A. Lassen, O. Munck and E. R. Tottey
Copenhagen, Denmark

A modification of *Kety* and *Schmidt*'s (1) technique for determining the cerebral blood flow and oxygen consumption employing krypton 85 instead of nitrous oxide was described (2).

Nine normal individuals were examined. Normality was controlled psychologically in 7 cases on the basis of Goldstein's cube test, and according to whether or not there were pathological undulations in learning digits. Clinically the patients' mental functions manifested no abnormalities.

Bilateral determinations of the cerebral oxygen consumption gave values from 3.2–3.6 cc O_2/100 g brain tissue/min., the mean value being 3.4 cc O_2/100 g/min., with a standard deviation of 0.16 cc O_2/100 g/min.

As this variation is within the limits of the experimental error (2), the cerebral oxygen consumption is a constant value in normal individuals.

The technique employed defines 100 g brain tissue as 100 g of the tissue draining via the superior bulbs of the internal jugular veins, viz. mainly grey and white matter, and besides meninges, spinal fluid, and partly the eyes.

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THE CEREBRAL OXYGEN CONSUMPTION IN PATIENTS WITH ORGANIC DEMENTIA DETERMINED BY USE OF RADIOACTIVE KRYPTON

By

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The relation between cerebral oxygen consumption and mental functions was studied in 10 cases of organic dementia, comprising 5 patients with cortical atrophy (disclosed by AEG), 3 with cerebral arteriosclerosis, 1 with cerebral lues, and 1 with hypertensive encephalopathy.

Although all patients showed definite signs of dementia, all but one could manage personal requirements and routine work, though not their normal occupation.

The patients showed typical anomalies on Goldstein's cube test (details to be published in Acta Psych. et Neurol. Scand.).

Bilateral determination of the cerebral oxygen consumption gave values from 1.6–2.8 cc O_2/100 g brain tissue/min. Thus there was no overlapping with the normal group.

As the cerebral cortex has a higher oxygen uptake than the white matter, a low cerebral oxygen consumption seems to indicate a diffuse cortical affection.

Presumably bilateral measurements of cerebral oxygen consumption with reliable techniques may be of value for the diagnosis of diffuse cortical atrophy in the individual subject.

Discussion: *M. Fog, G. H. Monrad-Krohn, O. Munck, M. Fog, O. Munck, G. H. Monrad-Krohn, M. Fog, K. Winther.*

CLINICO-PATHOLOGICAL OBSERVATIONS IN ANOXIA WITH DIFFERENT ETIOLOGY AND EFFECT

By

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In our large surgical clinics cases with more or less acute anoxia are often encountered. Several causes of anoxia may be combined, and it is supposed that the result may be an aggravation of the insult to the nervous tissue.

One might possibly improve the situation by eliminating one of the causes. The effect of chlorpromazin on cases with cerebral contusions may be explained by its temporary depressive action on O_2 consumption and temperature.

3 cases are presented.

One was a woman, 43 years old, who recovered completely after about 12 hours' unconsciousness following anoxia by hanging.

The second was a 34 year old man who died 48 hours after a contusion with an epidural hematoma and circulatory disturbances, possibly combined with a histiotoxic effect of alcohol and trichlorethylene.

The third was a 4 year old girl who survived 9 weeks after a traffic accident giving her a fracture in the frontal region. The elevated temperature was lowered by Largactil. After 6 weeks a marked brain atrophy resulted and histopathologically the picture was very much like that of a severe cerebral anoxia.

In the first case the vascular reaction had been moderate. In the second case the primary vascular reaction had been followed by tissue ischemia; maybe also a histiotoxic factor had been added. In the third case the vascular factor had provoked an extensive and progressive hypoxic situation in the brain.

DISCUSSION: *H. Seyffarth, Aa. C. Löken.*

CLINICAL OBSERVATIONS IN AN UNUSUAL CASE OF CEREBRAL ANOXIA

By

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In a boy aged 13 obstruction of the air passages by a foreign body caused a transitory arrest of heart action and respiration for approximately 10 minutes, after which he lived unconscious 4½ years until he died from an intestinal volvulus.

During this time there was no contact, no voluntary activity, only a very limited activity of other origin or reflectory type.

There was an increasing spasticity with the upper limbs in flexion, with the lower in extension and typical "pyramidal" deep and plantar reflexes and a pathological abdominal reflex with retraction of the whole abdominal wall. Normal pupillary reactions to light, corneal, palatal, pharyngeal, and coughing reflexes and snout and sucking reflexes were present. The retino-orbicular reflex of Cartesius and neck reflexes of Magnus de Klein could never be elicited.

The cochleo-orbicular reflex was present, gradually accompanied by a complex reaction like a startle response. A similar, less pronounced reaction could be provoked by stimuli of pain and strong light.

Of spontaneous activity purposeless conjugate eye movements, smacking, chewing, and swallowing movements and yawning were observed. Mostly the eyes were open, but sometimes closed giving an impression of natural sleep.

During the last 3 years he had seizures like typical "cerebellar fits".

The last years secondary sex characters developed.

Gross examination of the brain showed very pronounced bilateral atrophy of the cortex of the occipital and adjacent parts of the parietal lobes, less prononced of the frontal lobes while the central sulci and the temporal lobes seemed normal.

By sections through the brain a monstrous atrophy with a corresponding enlargement of the ventricular system was seen, the corpus callosum and the thalamic region almost disappeared.

At microscopic examination the nerve tissue within the most affected areas proved to be replaced by glial tissue.

(Previously a report of this case was given by Professor G. H. Monrad-Krohn in "Acta Psychiatrica et Neurologica Scandinavica", Vol. XXVII, 1952. The neuropathological examination was carried out by Dr. Aa. Christie Löken, who is preparing a detailed report.

The EEG findings have been reported by Dr. Arne Lundervold).

ANOXIA CEREBRI. AN ELECTROENCEPHALOGRAPHIC INVESTIGATION

By

Arne Lundervold
Oslo, Norway

The detailed neurological and laboratory data of this patient were reported at the congress by Odd Lindahl.

A 13 year old male accidentally had his larynx obstructed by a foreign body in August 1950. For 10 to 15 min. there was no heart action or breathing. The foreign body was removed under artificial respiration, and after 1 hour normal heart and lung function was restored. Since then the patient was without spontaneous movements and there was no evidence that he was aware of his surroundings.

From September 1951 the patient had seizures. A total of 33 electroencephalograms was obtained with a Kaiser 8 channel EEG apparatus. Stroboscopic stimulation and auditory stimulation were used regularly.

The first EEG showed a marked depression of all electrical activity. Slow waves appeared 2 months after the accident. They increased in voltage during the following 3½ years and their frequency decreased. Maximum amplitude was 300 micro V.

Seizure patterns were observed about 2 years after the accident. They started with spikes and a short time after bilateral spike and waves appeared. During the following 2 years more and more epileptic activity was registered. Then the seizure pattern disappeared and the slow waves became faster as well as decreased in voltage. When the boy died 4½ years after the accident the frequency was 7/sec. and the amplitude 40 micro V.

DISCUSSION: *G. H. Monrad-Krohn, N. A. Lassen, O. Munck, Aa. C. Löken, P. Tottey, G. H. Monrad-Krohn, K. Winther.*

FINAL DISCUSSION OF CEREBRAL ANOXIA: *M. Fog, E. Christensen, H. Seyffarth, G. H. Monrad-Krohn, E. Christensen, G. H. Monrad-Krohn, S. Tejning.*

Mogens Fog (Copenhagen, Denmark):

This discussion has valuably contributed to our knowledge of cerebral anoxia, but at the same time it has pointed to both theoretical and practical problems which have not yet been solved. I shall only mention a few of these.

In spite of Dr. Erna Christensen's conclusion, that it is the degree, not the type of anoxia which decides the pathological damages, I still feel convinced that further studies may reveal a different correlation between for example long-time hypoxia during the prenatal period and its consequences on the one hand, and the clinical and pathoanatomical effects of strangulation on the other.

In general, it is evident that neurological sequelae to chronic hypoxia of moderate degrees have not yet been fully evaluated.

The studies of perinatal anoxia and of the cumulative factors which can lead to anoxic conditions during anesthesia must stimulate to further attempts in preventive measures through a collaboration between neurologists, obstetricians, and anesthesiologists.

Some investigations (*Lassen* and *Munck*) suggest that we should not accept too easily the role of anoxemia in producing a variety of cerebral diseases. It seems as if some cases which have hitherto been considered primarily due to anoxia, in fact depend on a primary disturbance of cellular metabolism, and only secondarily produce a reduction of oxygen consumption.

So in various ways the theme has emphasized that anoxia is a fertile field of neurology.

Stig Tejning (Lund, Sweden):

Am Staatlichen Volksgesundheitsinstitut führt Dr. M-L Lingen Untersuchungen über den Einfluss von niedrigen Kohlenoxydhaemoglobingehalten auf die Flimmerfusion.

Sie stellte fest, dass so niedrige Kohlenoxydhaemoglobinkonzentrationen, dass sie bei bestimmten Personen keine oder nur unwesentliche subjektive Symptome hervorriefen, Flimmerfusionssenkung bzw. eine positive Evipanprobe ergaben.

2 von 10 gesunden Versuchspersonen, die mit Kohlenoxyd bis zu 10 % COHb exponiert wurden, zeigten eine einige Stunden lang anhaltende Senkung der Flimmerfusion.

11 von 21 gesunden Versuchspersonen, die bis zu 18 % COHb exponiert wurden, zeigten eine den Expositionstag lang dauernde Senkung der Flimmerfusion. Vier dieser Personen wiesen ausserdem eine positive Evipanprobe (Berg, 1949) vor, die jedoch erst 12–16 Std. nach der Exposition in Erscheinung trat – also nachdem das Kohlenoxyd aus dem Blut ausgelüftet war.

Von 6 Versuchspersonen, die an 2–4 Tage täglich einmal bis zu 8–10 % COHb exponiert wurden, zeigten alle zwischen dem 3. und 5. Tage eine etwa einen Tag lang anhaltende positive Evipanprobe.

26 Personen mit neurasthenischen Insuffizienzzuständen (sog. „chronische Kohlenoxydvergiftung“) wurden bis zu 10 %COHb exponiert. Bei 9 von diesen wurde am Expositionstag Flimmerfusionssenkung und am folgenden Tage eine positive Evipanprobe festgestellt.

Die positive Evipanprobe erschien somit nicht parallell der aktuellen Herabsetzung der Sauerstofftransportfähigkeit des Blutes. Zum Vergleich mit den oben stehenden Versuchen wurde der Einfluss von verminderter Sauerstoffspannung (Respiration von 12 % O_2 in N_2) an zwei gesunden Personen untersucht, die *während der bestehenden Hypoxie* sowohl Flimmerfusionssenkung als auch eine positive Evipanprobe zeigten. Nach beendeter Exposition mit sauerstoffarmer Luft konnten diese Veränderungen nicht länger nachgewiesen werden.

M-L Lingen hat ausserdem gezeigt, dass bei einer positiven Evipanprobe diese an einem Auge durch Applikation von Strychnin im Konjunktivalsack eliminiert werden konnte. (Vgl. *Seitz,* Arch. Psychol. 1940, 257).

Miscellaneous Papers

FIBER CONNECTIONS OF THE BRAIN STEM WITH PARTICULAR REFERENCE TO THE RETICULAR ACTIVATING SYSTEM

By

ALF BRODAL
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Some principal points in the structural organization of the pontine and medullary reticular formation were discussed, with particular reference to the lecturer's own experimental studies on ascending and descending fibers from the reticular formation. Several of the anatomical data indicate that the current conception of the organization of the "ascending activating system" needs revision.

The main points in this lecture have been incorporated in an introductory lecture delivered before the International Meeting of Neurobiologists in Groningen, August 1955: "Anatomical aspects of the pons and medulla oblongata", to be published in the Folia Psychiatrica, Neurologica et Neurochirurgica Neerlandica.

The original investigations referred to are the following:
A. Brodal and *G. F. Rossi:* Ascending fibers in brain stem reticular formation of cat. A.M.A. Arch. Neurol. & Psychiatr. *74*: 68–87, 1955; *G. F. Rossi* and *A. Brodal:* Cortico-fugal fibres to the brain stem reticular formation. An experimental study in the cat. J. Anat. *90*: 42–62, 1956. *A. Torvik* and *A. Brodal:* The origin of reticulospinal fibers in the cat. (In preparation).

DISCUSSION: *K. Krabbe, A. Brodal, R. Granit, A. Brodal, G. Magnussen, A. Brodal.*

SPASTICITY AND TEMPORAL SUMMATION—THE RÔLE OF MUSCLE AFFERENTS

By

R. GRANIT
Stockholm, Sweden

DISCUSSION: *T. Broman, H. Seyffarth, R. Granit, A. Brodal, R. Granit.*

NEUROSECRETION

By

B. HANSTRÖM
Lund, Sweden

(Published in: 1) Statens naturvetenskapliga Forskningsråds Årbok, p. 34, 1953–54; 2) Acta neurovegetativa VIII, 3, p. 269, 1954).

DISCUSSION: *K. Krabbe, B. Hanström, E. Christensen, B. Hanström.*

STEREOTAXIC BRAIN OPERATIONS

By

L. LEKSELL
Lund, Sweden

PROBLEMS IN NEUROEMBRYOLOGY

By

B. KÄLLÉN
Lund, Sweden

DISCUSSION: *G. Wohlfart.*

COLOUR DIFFERENTIATION IN THE VISUAL CORTEX OF THE CAT

By

DAVID H. INGVAR
Stockholm, Sweden

The spectral sensitivity of the retina of the cat has been compared with that of its visual cortex. This comparison refers to the same experiment and the state of full dark adaptation (*cerveau isolé* preparations). One eye, rigidly fixed, was stimulated with intermittent monochromatic light of variable intensity (tungsten filament lamp, Hilger-Tutton monochromator).

The retinal spectral sensitivity curve is defined as the energy reciprocals to constant ERG amplitudes in different wave-lengths, the ERG being measured according to the electrical resonance method of *Granit* and *Wirth* (1953). The cortical spectral sensitivity curve was calculated from the energy reciprocals to cortical evoked potentials of the same amplitude or latency in different wave-lengths. The cortical potentials were recorded from the exposed visual area with small platinum surface electrodes and photographed in 30–40 superimposed pictures.

The retinal sensitivity curves often coincided with the visual purple curve; usually there was a definite shift of the maximum towards the blue side. The cortical sensitivity curves deviated from the retinal ones, to an amount depending upon the energy level chosen. At certain energy levels, i.e. for selected equal cortical amplitudes or latencies in all wave-lengths, a highly increased sensitivity would appear in the blue (4500 to 4800 Å), the green (5300 Å), or also, though less pronounced, in the red part of the spectrum. At other energy levels the cortical sensitivity curves coincided with the peripheral retinal curves, i.e. the visual purple curve.

The results indicate that retinal mechanisms for brightness and wave-length discrimination in the cat (cf. *Granit* 1955) may also be demonstrated in the visual cortex.

DISCUSSION: *R. Granit, T. Bingley-Wennström.*

THE FUNCTIONAL ORGANIZATION OF THE DORSAL SPINOCEREBELLAR TRACT

By

A. LUNDBERG
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DISCUSSION: *A. Brodal, R. Granit, A. Lundberg, R. Granit, A. Brodal, A. Lundberg, R. Granit, A. Brodal, E. Kugelberg, A. Lundberg.*

FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

An electroencephalographic and clinical study. Preliminary report.

By

J. Presthus, S. Refsum, Aa. Skulstad and S. Östensjö
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Fourteen and six per second positive spikes constitute a well characterized electroencephalographic pattern, which was first described by *Erna* and *Frederic Gibbs* in 1948 and 1951 (Atlas of Electroencephalography, Vol. II, Addison-Wesley Press, Cambridge, Massachusetts 1952).

In the Department of Neurology, University of Bergen Hospital, 1463 patients have since 1953 been recorded during sleep. The recording technique described by the *Gibbses* was used. Fourteen and six per second positive spikes without any other paroxysmal discharge were observed in 38 patients, i.e. 2.6 per cent. (Fig. 1). The rhythm occurred in spontaneous sleep as well as in sleep induced by barbiturates. In a few cases it also occurred in the waking state. Twenty of the patients were above the age of twenty.

In some patients moderate focal changes were found and in a few cases a slight generalized dysrhythmia. In the majority of cases (22) no other pathological activity was recorded either in the waking state or in sleep.

A great variety of symptoms were noted in these patients. The most common complaints were: headache 16 patients; dizziness 15; grand mal seizures 14 (in 5 patients combined with psychomotor seizures); gastro-intestinal symptoms 8; behaviour disturbances (rage attacks) 5; syncope 4; anxiety 4; hypersomnia 4; vasomotor disturbances 4.

Other complaints were dysesthesias, hallucinations, tinnitus, attacks of dyspnoea, and attacks of sweating. Sometimes the symptoms were not too well defined. Frequently two or more symptoms were present in the same patient. In the majority of cases the symptoms were paroxysmal in nature. One patient had a diabetes insipidus which had occurred after a head injury, with a diuresis of 7½ liter in 24 hours.

As a possible etiological factor head injury with concussion was encountered in 10 patients, head injury with questionable concussion in 4 patients. Two patients had had an encephalitis.

A follow-up study of the patients with 14 and 6 per second spikes is being made with particularly regard to the effect of treatment and the prognosis.

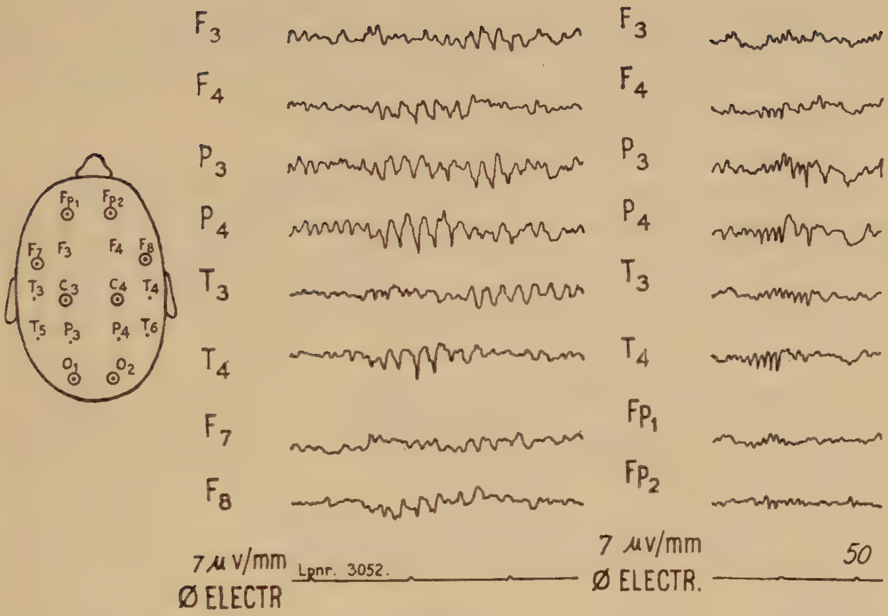
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Fig. 1.

The first part of the record shows 6 per second positive spikes in the right hemisphere, most marked in the parietal and in the temporal region. The second part of the record from the same patient, shows 14 per second positive spikes, occurring in the right as well as in the left hemisphere.

There can be no doubt that the 14 and 6 per second positive spikes constitute a well characterized electroencephalographic pattern. The problems which can be discussed are: What is the origin and the neurophysiological mechanism of this rhythm and what clinical importance does it have? It is hoped that further clinical studies may contribute to the elucidation of the last question.

Discussion: *T. Dalsgaard-Nielsen, S. Refsum, E. Kugelberg, S. Refsum.*

SACRAL ROOT SYNDROMES

By

E. Bohm, C. Frankeson and I. Petersén
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In 19 patients, the indication for exploration of the sacral nerve roots was rhizopathy symptoms associated with various organic changes in the region of the lower pelvis (urethrotrigonitis, prostato-vesiculitis, etc.). Stimulation of the sacral nerve roots was performed by pinching the nerves with a forceps. Following section or freeing of the roots, the pain diminished or disappeared and, in certain instances, surgery was followed by local healing of the organic disorder.

The following syndromes may be defined.

S II syndrome. Pain is encountered in the lumbar and groin regions, radiating to the posterior or inner aspect of the thigh (rarely to the knee), to the genitalia as well as the urinary tract. Involvement of the anus or perineum is exceptional. Intensification of pain occurs with certain activity, especially with rising from the sitting position and with coitus. Intensification of the pain with coughing and sneezing is unusual as is a positive Lasègue phenomenon. Parasthesia in the genital and gluteal region may be observed. Both reflex changes and pareses are absent. An associated urethrotrigonitis in woman and prostatovesiculitis in the male was noted in the majority of the patients.

S III syndrome. While groin and thigh pain may, as in the S II syndrome, be encountered, the pain is more often referred to the genitalia and anus.

S IV–S V syndrome. Pain in the anus, perineum, and coccyx. Many instances of so-called coccygodynia are contained in this category.

Discussion: *B. Silfverskiöld, I. Petersén, E. Kugelberg, E. Bohm.*

A NEW METHOD FOR REGISTRATION AND ANALYSIS OF NYSTAGMUS

By

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OPTOKINETIC NYSTAGMUS IN BRAIN LESIONS

By

P. Enoksson
Lund, Sweden

(To be published in the Acta ophthalmologica).

Discussion: *R. Granit, P. Enoksson, N. G. Henriksson, E. Kugelberg, P. Enoksson.*

ORGANIZATION OF NEUROLOGICAL REHABILITATION

By

T. Broman
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(Published in: Socialmedicinsk Tidskrift 8/55).

Discussion: *E. Busch, P. Paulsen, T. Dalsgaard-Nielsen, H. Seyffarth, Höök, G. Wohlfart, T. Broman.*

ACTH-CORTISONE TREATMENT OF DISSEMINATED SCLEROSIS

By

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36 patients suffering from disseminated sclerosis, representing the stages of the disease between purely monosymptomatic and totally incapacitated cases, have for 10 months been treated with ACTH-cortisone under regular and neurological control. Primarily the patients have been treated during hospitalization for three weeks with ACTH 60 mg per day, decreasing to 30 mg per day and gradually supplemented by cortisone, which then was administered in doses of 60–70 mg per day for 10 months.

The great majority of the patients presented the well-known biological reactions to the supply of hormone without deviations which could be correlated to the progress of the disease.

The progress of the disease during the observation period was registered by means of given definitions of the attack and its various qualities and compared with a corresponding selected and observed material of 60 patients not treated.

The 36 patients treated, during the 10 months developed a total of 45 attacks according to the given definition, and a total of 112 single symptoms manifested themselves, either as hitherto unknown to the patients *or* as a marked intensification of already existing symptoms *or* as recurrence of previously known, but remitted symptoms.

It may be concluded that the treatment had no favourable influence on the progress of the disease as compared with the spontaneous course. The frequency of attacks was not reduced. New symptoms appeared and previous symptoms were intensified or recurred independently of the treatment. The various attacks disable the patients or remit in accordance with the previous types of the disease—independently of the treatment. On the other hand there are no decisive reasons for the view that the treatment should have injured the patients.

DISCUSSION: *R. Müller, P. Thygesen.*

THE FLICKER FUSION TEST IN MULTIPLE SCLEROSIS

By

OLE BERG
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The flicker fusion threshold for a given person is normally stable and the same for both eyes. The normal range of variation of the critical flicker fusion threshold (CFF) is fairly narrow.

Analysis of the results of flicker fusion tests carried out during a 1–5 year follow-up of 100 patients with multiple sclerosis showed as follows. The CFF varied pathologically in 65 per cent. of the patients; it was abnormally low in 57 per cent.; and it differed from one eye to the other in 60 per cent. In a total of 77 per cent. the CFF was abnormal in some respect (varying and/or low and/or not the same for both eyes).

The evipan flicker fusion test (determination of the CFF after the intravenous injection of 5–10 cg evipan) was carried out in all cases. A positive evipan test indicating active, diffuse cerebral injury was noted in 75 per cent. of the cases during some period of the disease. During exacerbations the CFF often descended and the evipan tests were positive: conversely, during remissions the CFF ascended towards normal and the evipan tests turned negative. The test is of diagnostic value and useful for evaluating the activity of the disease.

DISCUSSION: *T. Broman, R. Müller, M. Milfeldt, N. G. Henriksson, G. Wohlfart, O. Berg.*

DIAMOX IN THE TREATMENT OF EPILEPSY

By

V. Fuglsang-Frederiksen
Odense, Denmark

27 epileptic patients ranging in age from one to 48 years were treated during a period from one to six months. The great majority of the patients had proved unresponsive to the current anti-epileptic drugs. Diamox was gradually introduced in addition to previous medication, part of this eventually being exchanged for Diamox. The dose varied between 250 and 1,000 mg. The *results* were: Marked improvement: 6 (1, 2, 1, 2) (numbers in brackets referring to type of seizure viz. grand mal, petit mal, psychomotor seizure, focal seizure). Improvement less than 75 %: 6 (0, 4, 1, 1). No change: 6 (0, 5, 1, 0). In two cases (0, 2, 0, 0) the severity of the disease increased and in the remaining seven cases no evaluation was possible as yet. It is of interest to note that in 4 of the 6 cases labelled "no change" a marked, but transient improvement was observed.

The electroencephalogram was highly abnormal in 9 cases, moderately abnormal in 13, and slightly abnormal in 5 cases before the treatment. 21 patients were reexamined during the treatment with Diamox and marked improvement of their EEG was seen in 12 cases, slight improvement in 6, while increasing EEG abnormalities were seen in 3 cases. In most cases the change of the EEG during treatment corresponded well with the clinical response.

Toxicity: No serious secondary effects were observed. One patient complained of slight gastrointestinal upset and another of dizziness early in the treatment. Two patients had tingling of the fingers, disappearing after a slight reduction of the dose of Diamox.

Discussion: *Simonsen, Fuglsang-Frederiksen.*

ELECTROPHORETIC STUDIES ON THE CEREBROSPINAL FLUID

By

Ingrid Gottfries and Sven J. Dencker
Lund, Sweden

With a simple apparatus we have concentrated CSF proteins by means of ultrafiltration under excess of pressure. For 2–2½ hours 3–4 ml

CSF are concentrated at a pressure of 12–18 kg/cm^2. The reliability of our method has not yet been fully assessed, but it seems to be adequate. We find the following fractions consistently: the X- and albumin fractions; the α_1-, α_2-, β_1-, β_2-, and γ-globulin fractions. These have been measured with a densitometer.

A group of 75 psychiatric and neurological cases was investigated. The curves estimated as normal can be divided into two groups: one showing a definitely low, the other a distinct γ-globulin fraction. Using electrophoresis we have sometimes discovered pathological changes where other methods, e.g. mastix, have given normal values. The most common pathological finding is a curve with increased γ-globulin and simultaneously decreased albumin fraction. An isolated increase, which is probably pathological, of either α_2-, β_1- or β_2-globulins has been observed. The curve in its other aspects seems normal. The significance of this finding is not yet clear. There seems to be no correlation between pathological electrophoretic findings and any special clinical condition.

Lipid staining according to Swahn has been made in several cases. The β-globulin fraction generally found in serum is very low in CSF. But in one case of Froin's syndrome, the specimen from the spinal space above but not below the tumor showed a curve identical with that of serum. This indicates a penetration of the blood-brain barrier of this high-molecular globulin protein.

DISCUSSION: *H. Malmros, A. Lindau, S. Dencker, I. Gottfries.*

DEEP HYPOTHERMIA IN INTRACRANIAL SURGERY

By

N. LUNDBERG, K. NIELSEN and E. NILSSON
Lund, Sweden

DISCUSSION: *E. Busch, K. Winther, E. Christensen, K. Kristiansen, N. Lundberg.*

THE EFFECT OF HYPOTHERMIA ON LESIONS OF THE BLOOD-BRAIN BARRIER PRODUCED BY UMBRADIL

By

P. G. Jeppsson and K. Nielsen
Lund, Sweden

(An abstract will be published in the Transactions of the 2nd International Congress of Neuropathology (Excerpta Medica) 1955).

Discussion: *E. Christensen, T. Broman.*

SOME CASES OF ACUTE NEURITIS OF CRANIAL NERVES

By

Knud Winther
Copenhagen, Denmark

Virus infections in the central nervous system are characterized by episodic appearance and by a frequent variation in the manifestations.

During these eight years a good number of cases of the so-called *Vertigo epidemica* (or *Neuraxitis vertiginosa*) have been observed in Denmark as well as in Sweden. This complaint is perhaps an encephalitis with lesion of the vestibular nuclei or of the n. vestibularis. Often there is affection of other cranial nerves as well.

For several years a frequent occurrence of double-sided facial paralysis has been observed in cases of *Polyradiculitis infectiosa.* The author has seen 11 such cases. In one of these there was an isolated lesion of the two facial nerves. As the typical cerebrospinal fluid finding may be missing, especially at the late stages, the diagnosis may be difficult.

In recent years the author has seen a remarkably large number of cases of the otherwise rarely observed *acute neuritis of the trigeminus.* A survey of 14 cases is made, they were youngish persons, mainly women. The complaint is sometimes preceded by a cold, angina, or gingivitis. There are intense pains in one or more branches, besides paraesthesias, soreness of the branches of the nerves, reduced sensitivity in the face and perhaps in the cornea and the tongue as well. In a few cases other cranial nerves are affected, too. In some cases changes of the cerebrospinal fluid, a slight fever, and other general symptoms have been observed. The duration of the disease is from some weeks to several months. The pains have not the character of malignant neuralgia. There have not been any signs of herpes zoster, and it has been possible to exclude other organic nervous complaints. The author supposes that it is a case of virus infection, a "focal neuraxitis" in the trigeminus.

DISCUSSION: *G. Wohlfart, L. Welander, T. Broman, K. Winther.*

THE CONCEPTION FUNCTIONAL NEURITIS, ESPECIALLY OF THE UPPER EXTREMITIES

By
HENRIK SEYFFARTH
Oslo, Norway

Functional neuritis is caused by lesions at the point where the nerve is compressed through narrow passages and is the result of overstrain because of unvaried muscle work, generally psychomotor tension with a cramped manner of working.

Schematically the developments are:

1. myoses at lesion point with tenderness and increased consistency of the muscle.
2. subjective symptoms, fatigue and pain.
   (a) locally, surrounding the point of lesion.
   (b) corresponding to the spread of the nerve in muscle and skin.

TABLE 1
Functional neuritis.

Nerve	*Point of Lesion*	*Paresis*
n. medianus	m. pronator teres	M. opponens dig I a. o.
n. radialis r. prof.	m. supinator	Dorsalreflex. artic. carpi
n. radialis	sulcus spiralis	,, ,, ,,
n. axillaris	axillen	Supinat + abd. i artic. Humero-scapul.
Plexus brachial	m. scalen. med. (+ ant.) (+ costa I)	Diffuse
n. thoracal. long.	m. scalen. med. + post. (+ costa I)	By pressing the extended arm upwards
accesorius	m. st. cleido mast a. o.	Twisting of head shoulder lifting
n. hypoglossus	m. stylohyoid a. o.	Lingua, open the mouth

4. Paresthesia and later hypæsthesia (neuritis), with secondary myosis surrounding the points where the nerve ends. Paresis can often be detected before the subjective symptoms appear.

Procain injections near the site of nerve lesion will generally give immediate relief of the paresis before anæsthesia of the nerve itself will occur within ½–1 minute. Later the strength of the muscle reappears and is generally considerably greater than before. These injections render the muscles softer and less tender and they proved to be effective also where other treatment had been employed beforehand.

The treatment also includes massage, relaxation gymnastics, and training in the proper manner of working.

In Table 1 the most important types of functional neuritis are underlined. Functional neuritis is very often the cause of pain, but generally is not diagnosed as such before severe nerve lesions have occurred. This applies particularly to lesions of the plexus brachialis.

The investigation of 324 patients with functional neuritis showed a growing frequency with increase of age: 11–24 years of age: 90 patients, 25–39 yrs.: 181 patients, 40–55 yrs.: 255 patients.

DISCUSSION: *K. Winther, T. Broman, H. Seyffarth.*

VERTIGO POSITIONALIS

By

L. WELANDER

Gothenburg, Sweden

DISCUSSION: *B. Silfverskiöld, H. Seyffarth, A. Grönberg, B. Silfverskiöld, L. Welander.*

HYPNOCEPHALAEA CLINOSTATICA IN PATIENTS WITH MIGRAINE

By

T. DALSGAARD-NIELSEN

Copenhagen, Denmark

As a special group within the interparoxysmal morning headaches the author establishes a type of headache for which he suggests the term Hypnocephalaea clinostatica. The term is derived from ὕπνος = sleep, κεφαλή = head, πλίνη = bed, and στάσις = position.

Hypnocephalaea clinostatica is most frequently mistaken for actual attacks of migraine but is monophasic, as symptoms of the vasoconstrictor aura are absent. The patients feel that this headache is of a migraine-like nature, and this is verified by means of the author's percutaneous nitroglycerin test with which it is identified as vasodilator headache.

The author explains its occurrence as the result of an interaction of 3 factors:

(1) The clinostatic conditions during the horizontal position.

(2) Certain changes occurring in the organism during sleep; these two factors together lead to such changes in the distribution of tissue fluids, in muscle activity and in osmolarity that the conditions are present of an increased filling in the cephalic vessels and an increased transudation in these areas.

(3) The third factor to be considered is the special biological mode of reaction of the migraine organism, which includes the low vasodilator headache threshold demonstrated by the author and rendering the migraine organism especially vulnerable by the factors mentioned in (1) and (2).

Hypnocephalaea clinostatica occurs with great frequency. In the author's series of unquestionable cases of migraine ophthalmique, 66 per cent. thus had a headache of this type and, as it may occur daily through prolonged periods in many cases, it is much more disabling than are the attacks of actual migraine. In the author's opinion it may also occur in patients with other types of vasodilator headache with a low threshold, and, on the whole, in patients whose headache threshold is exceeded.

The therapeutical consequence of the author's argumentation is that it must be possible to counteract Hypnocephalaea clinostatica by (1) alteration of the horizontal position, (2) regulation of sleep, and (3) inhibition of the vasodilatation. The author has therefore treated the patients with 20 cm.'s elevation of the head of the bed, reduction of the duration of sleep, and prophylactic administration of a gynergen tablet at bedtime with good result.

DISCUSSION: *L. Welander, T. Dalsgaard-Nielsen.*

TESTS ON REACTION TO STRESS IN PATIENTS WITH A POSTCONCUSSIONAL SYNDROME

By

E. HØYRUP
Aarhus, Denmark

ACTIVE TREATMENT OF ACUTE HEAD INJURIES

By

RAGNAR MÜLLER and BENGT NAUMANN
Stockholm, Sweden

Since the beginning of 1953 the patients with acute head injuries admitted to Serafimerlasarettet in Stockholm have been treated with early ambulation and psychotherapy. The only treatment used beyond this has been surgical interventions, and prophylactic measures against meningitis in cases of complicated fractures.

The material consists of 258 consecutive cases, the patients being between 13 and 79 years of age. The amnesia lasted for a minimum of 1 hour in 43 %, and for more than 24 hours in 10 % of the cases. 23 % of the patients had fracture of the skull. Pretraumatic psychic disorders were recorded for 115 patients. Every 5th patient said that they had lived under psychic stress at the time of the accident. The material is representative of those head injuries that occur in a large town.

The patients began to be up and about as soon as their minds became clear and they were wholly or almost symptom-free as regards headache and giddiness. Nervousness, anxiety, difficulty of concentration or similar disorders have not been an indication for bed rest. Absolute recumbency has never been prescribed, except in those cases where there were signs of subarachnoid haemorrhage or intracerebral haematoma, and postoperatively. 53 % of the patients were ambulatory within the first three days, 88 % within the first week.

The verbal psychotherapy as a rule consist in reassurance, suggestion, and persuasion. Every 6th to 7th patient needed a more thorough treatment, at which neurotic conflicts were dealt with.

If those cases are excluded in which the hospital stay was essentially prolonged because of extracranial injuries, the maximum length of hospitalization was a fortnight in 88 % of the cases. The patients were not discharged from hospital until they had been able to be up and about throughout a whole day without any appreciable complaints.

After discharge the patients have rested at home for about a week and have subsequently been controlled as outpatients. Those who then had any complaints have attended the outpatient department twice or three times a week for psychotherapy.

The period of incapacity for those 234 patients who had no severe extracranial injuries was in 79 % less than 4 weeks. After 8 weeks nine only, or 4 %, were incapacitated. Eight of these have subsequently been crossed off the sick list. At the end of the period of incapacity all except three have resumed full work. Of the 24 who had severe extracranial injuries none had cranio-cerebral symptoms lasting for more than 8 weeks. For the saks of comparison it may be mentioned that in a Swedish material of 531 patients with conservatively treated head injuries the period of incapacity exceeded 8 weeks in 35 %, and 1 year in 9 % of the cases (*Müller*).

After a period of observation averaging 10 months the patients have been followed up. None had been incapacitated again during the period of observation. 233 patients did the same work as before the accident. 21 of these, however, complained of slight disorders in the form of headache, giddiness, nervousness, or difficulty of concentration. Six were slightly demented but subjectively symptom-free. In two patients a post-traumatic epilepsy had developed. Only four patients had reduced working ability as a result of the head injury. One of these was still hospitalized. The other three, of whom two were demented, were doing less skilled work.

Among those who at the follow-up stated that they had had troubles after the period of incapacity, in the form of headache, giddiness, nervousness, or difficulty of concentration, the frequency of pretraumatic psychic disorders and stress was significantly higher than among those who had been symptom-free. All the demented patients had sustained very severe head injuries.

RESULTS OF THE TREATMENT OF ACUTE HEAD INJURIES GUIDED WITH THE AID OF THE EVIPAN TEST

By

Erik Åkerlund
Falun, Sweden

At the Surgical Clinic, Malmö Allmänna Sjukhus, the treatment of patients with uncomplicated acute head injuries (commotio cerebri) is guided with the aid of the Evipan Test (determination of any changes in the flicker fusion value under the influence of evipan). The series consists of 254 patients seen at the department during 1954. As the hospital is the only one in a town with a population of 200,000, the series is representative as regards frequency as well as degree of severity.

The treatment had mainly been: bedrest as long as the test remains positive; during the convalescence control at the outpatient department, and in cases with a long duration of symptoms medical gymnastics. Special psychiatric treatment in only a few cases.

The duration of the evipan test, hospital attendance, and incapacity to work is summarized in the tables.

Duration of Evipan test.

Duration in days ..	0–7	8–14	15–21	22–	Not possible to perform	Total
Number of cases...	164	47	9	3	31	254

Hospital attendance.

Duration in days ..	1–7	8–14	15–21	22–	Total
Number of cases...	144	89	13	8	254

Incapacity to Work.

Duration in weeks	0–4	5–8	9–16	17–	Total
Number of cases...	176	51	17	10	254
Percentage	69	20	7	4	100

All but 2 uninsured housewives returned to their former work to its full extent.

FINAL DISCUSSION ABOUT HEAD INJURIES: *G. H. Monrad-Krohn, B. Silfverskiöld, E. Busch, R. Müller, K. Kristiansen, E. Höyrup, E. Åkerlund.*

Ragnar Müller:

To Dr. Silfverskiöld: We have never proclaimed ourselves to be the first to use early ambulation. As I said in the introduction, early physical activation after head injuries was introduced in many hospitals in Great Britain and the U.S.A. during the second World War. Prophylactic psychotherapy, on the other hand, which in our opinion and according to our present experiences is a very important part of the treatment, does not seem to have been systematically tried before. We have never had any difficulty in connection with the early ambulation or seen any ill-effects of it. On the contrary, the patients have been very happy to be up and about.

To Dr. Åkerlund: Our materials are not comparable, since Dr. Åkerlund has a greater number of cases of slight injuries. We have a duration of amnesia exceeding one hour in 43 % of the cases, Dr. Åkerlund in only 11 %. Nevertheless, 11 % of Dr. Åkerlund's patients were incapacitated after 8 weeks, while our figure is only

4 %. Furthermore, it seems to me that the period of observation in Dr. Åkerlund's cases was relatively short.

CEREBELLAR APOPLEXIES

By

B. DE FINE OLIVARIUS and C. F. BISGAARD-FRANTZEN
Copenhagen, Denmark

PROBLEMS CONCERNING ANTICOAGULATION TREATMENT OF CEREBRAL APOPLEXY

By

T. LYAGER, T. DALSGAARD-NIELSEN and E. SKINHØJ
Copenhagen, Denmark

1000 cases of cerebral apoplexy, comprising hæmorrhages as well as thromboses and embolisms, have been treated in the Neurological Department of Frederiksberg Municipal Hospital. Anticoagulation treatment of cerebral thrombosis is difficult as the differential diagnosis between hæmorrhage and thrombosis is uncertain.

At autopsy, it was found that 40 % of the cases clinically diagnosed as thromboses proved to be mæmorrhages, while 29 % of those diagnosed as hæmorrhages were thromboses.

The use of anticoagulation therapy is indicated by the fact that in 52 % of the cases intra- or extracranial thromboses were directly or indirectly the causes of death; in 15 %, extracranial thromboses alone were directly responsible and they were contributory in 27 %.

75 % of the extracranial thrombotic complications occurred in cerebral thrombosis and 25 % in cerebral hæmorrhage.

In the differential diagnosis, importance must be attached to the presence of blood in the cerebrospinal fluid. Cases with blood-stained cerebrospinal fluid are classified as cerebral hæmorrhage. Cases without blood in the cerebrospinal fluid are considered thromboses and some hæmorrhages. The latter must be excluded clinically in different ways.

Nevertheless a few cases of cerebral hæmorrhage remain in this group. Anticoagulation treatment has therefore been postponed until the third day, when the hæmorrhagic focus is considered to be established. As 45 % of the fatal cases of cerebral thromboses do not die from their condition until after the third day, and as most of the extracranial thrombophlebitic complications seldom appear within the first three days, a favourable anticoagulation effect is considered possible, even if the treatment has not been instituted on the first day.

Results of anticoagulation therapy will be published later.

Discussion: *N. C. Borberg, K. Krabbe, N. C. Borberg, K. Krabbe.*

EEG IN CEREBRAL APOPLEXY

By

B. Harvald and E. Skinhøj
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147 patients with apoplexy have been EEG-examined in order to decide if it is possible electroencephalographically to distinguish different subgroups; the result is shown in the table:

	Haemorrhage	Thrombosis	Embolism	Vascular spasm?	Haemorrhage? Thrombosis?
Severe focal abnormalities ..	9	8	4	1	16
Slight focal abnormalities ..	3	12	1	4	10
Severe diffuse abnormalities		5		3	2
Slight diffuse abnormalities	1	5		3	7
Normal	1	24	2	13	13
Total	14	54	7	24	48

The following conclusions are drawn:

(1) A normal or non-focally abnormal EEG makes the diagnosis of haemorrhage highly improbable.

(2) Severe focal abnormalities are most probably due to haemorrhage.

(3) Slight focal abnormalities are most probably due to thrombosis.

Discussion: *V. Fuglsang-Frederiksen, B. Harvald, A. Lundervold.*

SYNDROME OF THE ANTERIOR SPINAL ARTERY

By

E. Skinhøj
Copenhagen, Denmark

The writer has earlier reported the cases of three patients which seemed to form the clinical counterpart to E. Krogh's experiments on hypoxia of anterior horn cells.

Including a fourth case with exactly the same symptomatology I shall try to sum up the clinical picture of what is supposed to be a pure syndrome of the anterior spinal artery on an arteriosclerotic basis.

In connection with an x-ray demonstrable arteriosclerosis of the lumbar aorta the patients over a period of years develop a pure and quite monosymptomatic nuclear paresis of both legs with the special distribution that the antigravity muscles are last and least affected. There must be no afferent symptoms, no sphincteral disturbances, no symptoms from the pyramidal tract, no signs of peripheral vascular insufficiency, the blood status and blod sugar level must be normal, Wassermann reaction negative, and the anterior horn cell origin must be certified by electromyography and biopsy of the muscles.

In my cases there were no fasciculations of the muscles.

The spinal fluid was normal or with slight hyperalbuminosis.

If the onset has been more abrupt, for instance by thromboses or by luic entarteritis there may in addition be pyramidal symptoms and fasciculations, i.e. the clinical picture of amyotrophic lateral sclerosis.

Discussion: *M. Milfeldt, E. Skinhøj.*

HYDROMYELIA IN NEW-BORN INFANTS

By

A. Wangel
Helsinki, Finland

Discussion: *E. Christensen, A. Wangel.*

ON THE GENESIS OF CYSTS IN THE CENTRAL NERVOUS SYSTEM

By

G. Wangel
Helsinki, Finland

Discussion: *E. Christensen.*

ON STATIC-ATACTIC FUNCTIONAL DISORDERS CAUSED BY ALCOHOL

A comparative study

By

T. A. Pihkanen
Helsinki, Finland

With an alcohol dose of one gram of absolute alcohol per kilogram body weight, taken in even quantities in the course of an hour on an empty stomach, static ataxia in two test series has been determined by applying a modified Romberg Test. In the first series the alcohol is taken as blended brandy (strong drink, 32,6 per cent (w/w)), in the second as beer (malt drink, 3,6 per cent (w/w)). In the strong drink series, the increase in static ataxia was nearly double that in the malt drink series. Also the peak disorder manifested itself earlier in the former series. Individual differences in the reaction are considerable.

FROM THE DEPARTMENT OF PHYSIOLOGY, KAROLINSKA INSTITUTET, THE NEUROSURGICAL CLINIC, SERAFIMERLASARETTET, AND THE CLINIC FOR CONVULSIVE DISORDERS, STORA SKÖNDAL, STOCKHOLM

THE EFFECT OF INTRAVENOUS XYLOCAIN[1] ON THE CORTICAL SEIZURE ACTIVITY EVOKED BY INTERMITTENT PHOTIC STIMULATION IN EPILEPTICS

By

C. G. BERNHARD, E. BOHM, S. HÖJEBERG, and K. A. MELIN

In experiments on cats and monkeys *Bernhard* and *Bohm* (1954 a and b, 1955) studied the effects of different local anaesthetics on the electrially evoked epileptiform cortical after-discharge and related corticospinal phenomena, and compared them with the effects of these drugs on spinal reflex functions and ascending transmission mechanisms. The experiments showed that local anaesthetics have a specific anticonvulsive effect. Intravenous injections of these substances in doses which do not alter the non-convulsive EEG, reduce or abolish the poststimulatory epileptiform cortical after-discharge. Among the different local anaesthetics tested xylocain showed a favourable relation between anticonvulsive effect and toxicity, and doses which abolished the experimental epileptic attack were found to have no influence on the blood pressure. On the basis of these experiments xylocain was used clinically as an anticonvulsant in cases of status epilepticus, and it was found that intravenous injection of xylocain stopped the convulsions (*Bernhard, Bohm* 1954 a and b, *Bernhard, Bohm, Höjeberg* 1955). In their animal experiments *Bernhard* and *Bohm* (1955) also showed that injections of barbiturates in doses too small to cause sedation or influence the epileptic cortical activity increased the anti-epileptic effect of xylocain. This summation effect could also be demonstrated in the clinical investigations (*Bernhard, Bohm,* and *Höjeberg* 1955).

Since it was found that the status epilepticus can be abolished by intravenous injections of xylocain it was of interest to investigate its effect on a seizure activity provoked by sensory stimulation in epileptics. Intermittent photic stimulation has been used by many authors for studying epileptic processes (see *e.g. Walter et al.* 1948, *Gastaut et al.* 1948, *Gastaut* and *Hunter* 1950, *Rodin et al.* 1955, *Mundy Castle* 1953) and it has been shown that in some patients with latent or manifest epilepsy intermittent photic stimulation evokes a seizure activity. This activity is characterized by a bilateral multiple spike-and-wave or 3 per second wave-and-spike pattern. Sometimes the photic stimulation provokes disturbances of consciousness of short duration or rhythmical twitches of a myoclonus type in the upper extremities. Occasionally a grand mal attack may be induced. As a rule photic stimulation carries little risks for the patient.

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[1] Xylocain is the trade name of the producer, the Astra Pharmaceuthical Company, Sweden. The nonproprietary names are lignocaine and lidocaine. In these investigations the pure substance xylocain was used.

In the present investigations we have studied the anti-epileptic effect of intravenous xylocain on the cortical seizure activity provoked by this method in epileptics. Since in the animal experiments it was found that xylocain in doses which abolish the electrically evoked epileptic cortical activity does not influence the non-convulsive EEG, the effect of intravenous xylocain on the EEG in normal humans was also studied. Finally investigations were performed in order to demonstrate the summation effect of barbiturates and xylocain.

METHOD AND MATERIAL

The EEG recordings were made in a semidarkened room, with the patients in a sitting position. Ag-AgCl-electrodes were used, and both scalp-to-scalp as scalp-to-ear-linkages were used. The leads are shown on diagrams on the published records. Recordings were made with an eight-channel Schwartzer electroencephalograph, with a time constant of 0.3 sec.

Photic stimulation was performed with a Kaiser photo-stimulator. The duration of the flashes at peak intensity was about 50 microsec. and the rate of the flashes could be varied from one to thirty flashes per sec. Sometimes double flashes were used, with an interval of 50 or 100 msec.

The material consisted of 5 normal cases and 15 epileptics. Among the epileptics 7 responded with seizure activity on photic stimulation. The patients suffered from severe epilepsy and showed several epileptic manifestations (grand mal and petit mal attacks). They were permanently hospitalized at the Clinic for Convulsive Disorders, Stora Sköndal. During the time for the investigations the patients received antiepileptic drugs (barbiturates, hydantoin and oxazolidin derivates) in order not to disturb the balance in their condition. The age of the patients varied between 15 to 55 years.

Xylocain (1 and 2 per cent solution) was used *without epinephrine* and the doses varied between 1 and 8 mg./kg. The drug was injected intravenously for 3 to 6 min. under careful observation of the patient and control of the blood pressure and the pulse rate. In the investigations on the summation effect of barbiturates and xylocain intravenous Hypnofen (20 per cent solution of allypropymal and diemal) was used.

RESULTS

I. *The effect of intravenous xylocain on the EEG in normal subjects*

The investigations include 5 subjects, the ages ranging between 20 and 40 years. In the personal and family histories there were no neurological diseases and at the time for the investigations the neurological examination was without pathological findings.

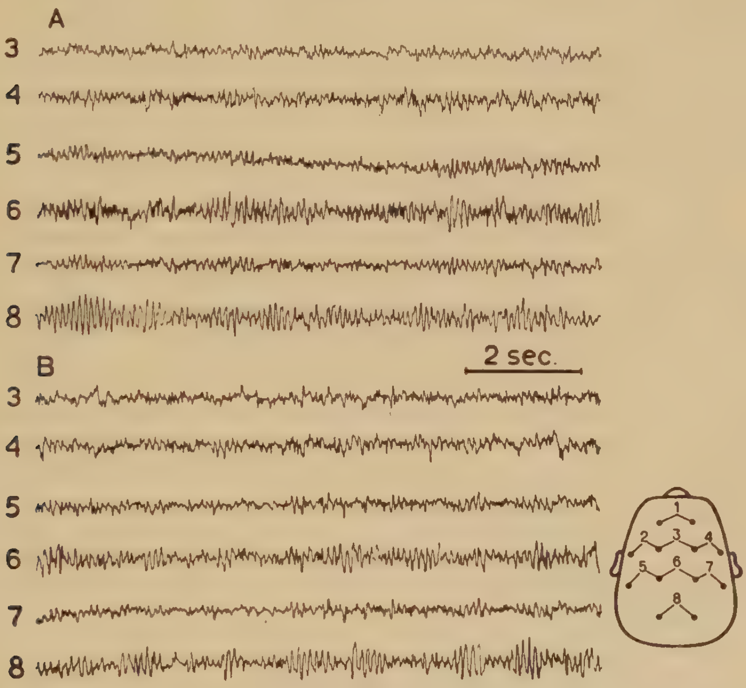

Fig. 1.

Normal case. A, cortical activity before the injection, and B, after the intravenous injection of 6 mg./kg. xylocain. The position of the electrodes is shown in the diagram.

Xylocain was given intravenously in doses varying between 2 and 8 mg./kg. body weight. Thus, in one subject 2 mg./kg., in two subjects 4 mg./kg., and finally in two subjects 8 mg./kg. xylocain were injected.

In all subjects except for one the EEG was not influenced by the injections. Fig. 1 demonstrates the EEG records (A) before and (B) 2 minutes after the injection of xylocain (6 mg./kg.). As can be seen, neither the frequency nor the amplitude of the cortical activity was significantly altered by the intravenous injection of xylocain.

One subject in which 4 mg./kg. xylocain were injected showed slight EEG changes mainly characterized by a decrease of the amplitude. This change occurred at the end of the injection and lasted for about 10 minutes. During the injection there was an increase in the pulse rate from 80 to 100/min. in connection with a certain anxiety.

In all cases except for two the subjects complained of a slight feeling of "dizziness, heat in the body, tingling in the lips or extremities." These symptoms have been described earlier after intravenous injections of local anaesthetics (see e.g. *Graubard* and *Peterson,* 1951). Usually these effects ocurred at the end of the injections and disappeared after 5 to 10 minutes.

No sedative effect of the xylocain in the doses used was noticed, nor was there any significant effect on the blood pressure or the pulse rate.

II. *The effect of intravenous xylocain on the cortical seizure activity in epileptics induced by intermittent photic stimulation*

In seven epileptics who responded to photic stimulation, xylocain was injected intravenously on 15 occasions. Fig. 2 illustrates the typical effect of xylocain on the provoked cortical activity. The patient was a 22 year old man who had suffered from epileptic attacks of grand mal and petit mal type since 15 years of age. Record A in Fig. 2 shows the provoked seizure activity before the injection of xylocain. Records B and C were taken 5 and 10 minutes after the injection of xylocain (4 mg./kg) and show that the photic stimulation did not evoke any seizure activity. Record 2 D demonstrates that the evoked seizure activity appeared again 22 minutes after the injection, but that it only appeared in the postcentral regions. Record 2 E, finally, shows that 30 minutes after the injection the photic stimulation evoked seizure activity over the whole brain.

In all cases which responded to photic stimulation, the stimulation evoked bilateral synchronous seizure activity. In 14 experiments out of 15 the injection of xylocain was followed by an abolition of the evoked seizure activity within 2 or 3 minutes. The seizure activity elicited by photic stimulation was abolished during a period varying between 5 and 26 minutes. The seizure activity then reappeared and after 9 to 90 minutes after the injection it resumed the pre-injection pattern.

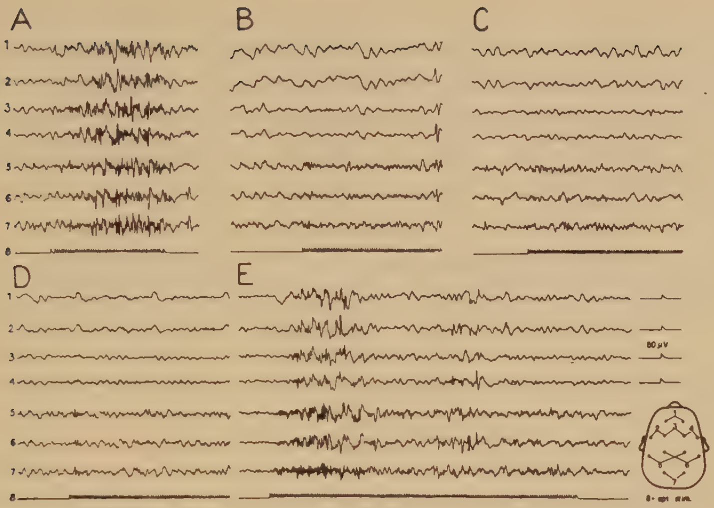

Fig. 2.

Epileptic patient. A, the seizure activity evoked by photic stimulation before injection. B and C shows the cortical activity 5 and 10 min. after the injection of 4 mg./kg. xylocain. Record D taken 22 min. after the injection, and record E obtained 30 min. after the injection. Calibration 50 µV. The position of the electrodes is shown in the diagram.

In five experiments the photic stimulation evoked clinical absences. Generally these absences were eliminated by xylocain during the period after the injection when the seizure activity was abolished, in order to return when the hypersynchronous cortical response to photic stimulation reappeared.

It was found that the abolishing effect on the evoked seizure activity generally increased with higher doses of xylocain, although there are considerable variations. For example, on one occasion, in one patient 1 mg./kg. of xylocain was enough to abolish the evoked seizure activity, but on two other occasions twice and three times the dose was necessary to obtain the same effect. In another case 2 mg./kg. on one occasion abolished the evoked seizure activity which before the injection was not followed by absences. One week later the patient suffered from frequent absences and photic stimulation regularly evoked an absences in connection with the seizure activity. Despite the xylocain dose being raised to 4 and 6 mg./kg. the seizure activity could not be completely abolished. On the other hand, the absences evoked by the photic stimulation could be eliminated for 10 minutes with a dose of 4 mg./kg. whereas 6 mg./kg. abolished the absences for 30 minutes.

Generally the seizure activity after being eliminated by the injection of xylocain first re-appeared in the post-central regions. One case, however, differed in this respect. Except for the cortical seizure activity the photic stimulation also evoked myoclonic twitches in the upper extremities. An injection of xylocain (2 mg./kg.) abolished the twitches as well as the cortical seizure activity. However, when the hypersynchronous activity returned, it was first recorded from the central cortical regions.

III. *The effect of xylocain and small doses of barbiturates on the seizure activity induced by photic stimulation in epileptics*

Only those cases in which the injection of 1 mg./kg. of xylocain did not influence the evoked seizure activity, were used for these investigations (4 cases). The investigations were performed in the following

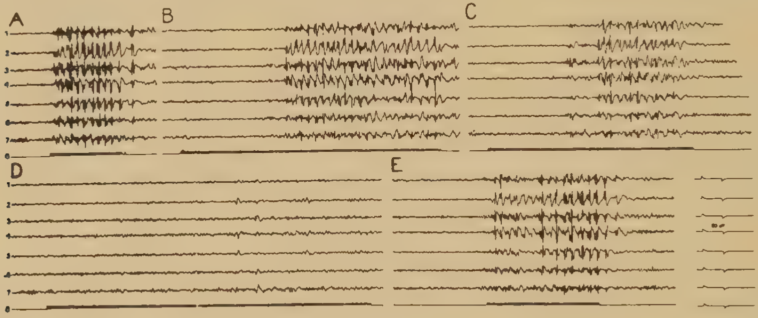

Fig. 3.

Epileptic patient. A, the cortical activity evoked by photic stimulation before injections. Record B, after intravenous injection of 1 mg./kg. xylocain. Record C taken 30 min. later and 5 min. after the intravenous injection of 0.5 cc Hypnofen. Record D obtained after the intravenous injection of 1 mg./kg. xylocain, and record E taken 12 min. after the last injection. Calibration 50 μV. For further explanation see text. The same electrode positions as in Fig. 2.

way. The seizure activity evoked by photic stimulation was recorded before the injection (Fig. 3 A). As mentioned above, 1 mg./kg. xylocain injected intravenously was found to be without effect on the evoked seizure activity (Fig. 3 B). After an interval of 30 minutes, permitting the xylocain to be eliminated, 0.5 ml Hypnofen was injected intravenously. This dose corresponds to 1.5 mg./kg. of barbiturates. The effect of photic stimulation was tested again and it was found that the Hypnofen injected had no influence on the evoked seizure activity either (Fig. 3 c). Five minutes later 1 mg./kg. of xylocain was again injected and this injection was followed by a total abolition of the seizure activity (Fig. 3 D). 12 minutes after the last xylocain injection the seizure activity reappeared (Fig. 3 E). Fig. 3 thus demonstrates the typical summation effect of barbiturates and xylocain in doses which alone did not influence the hypersynchronous activity.

On 5 occasions this summation effect was demonstrated on 4 patients. In no case it was found that the Hypnofen injection had any significant influence on the evoked cortical activity.

It should be mentioned that in one case a much larger dose of xylocain had to be injected in order to abolish the evoked cortical seizure. After the injection of the usual dose of 0.5 cc Hypnofen, 1 to 4 mg./kg. xylocain had no influence on the seizure activity. When the dose was raised to 6 mg./kg., a depressing effect was, however, obtained.

DISCUSSION

On the basis of examinations of the normal subjects we conclude that single intravenous injections of xylocain in doses up to 8 mg./kg. have no significant influence on the normal cortical activity. In one case the injection was followed by anxiety and an increased pulse rate, probably depending on the unpleasant feeling of heat and tickling which occurred in this case. We therefore regard the slight amplitude changes of the EEG as being secondary and not due to any direct action of the xylocain (4 mg./kg.) on the cortical activity. It should be pointed out that in two other cases even 8 mg./kg. did not influence the EEG. The conclusion that xylocain in doses up to 8 mg./kg. had no effect on the normal cortical activity is in agreement with our findings in animal experiments (*Bernhard* and *Bohm* 1955).

We did not find any significant changes of the interseizure EEG pattern in the epileptics in whom the evoked seizure activity was investigated in this study. This analysis, however, does not permit any conclusions as to the effect of xylocain on the dysrhytmic interseizure EEG, since on the occasions for the investigations the patients received the usual antiepileptic drugs for therapeutical reasons.

It is evident that small and moderate intravenous doses of a local anaesthetic like xylocain have an exquisite effect on the hypersynchronous widespread cortical seizure activity evoked by photic stimulation in epileptics. This is in conformity with the effect demonstrated on the electrically evoked epileptic cortical after-discharge in animals (*Bernhard* and *Bohm* 1954 a and b, 1955) and man (*Ottosson* 1955) and on the status epilepticus in man (*Bernhard, Bohm* 1954 a and b, *Bernhard, Bohm,* and *Höjeberg* 1955). In conformity with the results obtained in the animal experiments mentioned the investigations into the evoked seizure activity in epileptics show that the anticonvulsive effect of intravenously administered xylocain in the doses used is of short duration (maximum 30 minutes), as is also to be expected from what is known about the rapidity of the decomposition of the drug (see *Sung* and *Truant* 1954).

SUMMARY

(1) The effect of intravenous xylocain on the normal cortical activity was studied in 5 healthy subjects. Doses up to 8 mg./kg. were shown to have no influence on the EEG.

(2) The effect of intravenous xylocain on the cortical seizure activity evoked by photic stimulation was tested in seven epileptic patients on fifteen occasions. It was found that small and moderate doses of xylocain (1–8 mg./kg.) temporarily abolished the evoked seizure activity.

(3) In examinations of four epileptics it was shown that a small dose of barbiturate increased the effect of intravenous xylocain.

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FROM THE HOSPITAL FOR INFECTIOUS DISEASES, JÖNKÖPING
(HEAD: DR. OLLE GABINUS)

THE FAMILIAL OCCURRENCE OF MULTIPLE SCLEROSIS

By

BENGT ESTBORN

The occurrence of more than one case of multiple sclerosis in a family has long been considered extremely rare. *Curtius* (1933) and, later, *Curtius & Speer* (1937) showed, however, in two studies from Bonn and Heidelberg that in a comparison with morbidity figures from Switzerland (*Ackermann,* 1931) there was a considerably higher incidence of multiple sclerosis among relatives of persons with the disease in Germany than in the general population in Switzerland. Among 656 relations—parents and siblings of 106 multiple sclerosis patients—they found 4 definite cases of the disease—that is, an incidence of 0.61 per cent, or more than 13 times the "double incidence" in the general population (0.023 per cent according to *Ackermann,* 1931). Moreover, they found among the relatives a remarkably large number of cases of other nervous diseases and mental disorders. *Curtius & Speer* summarized the results of their investigations in two points:

"From our figures it is clear that a *specific,* not an unspecific, disposition to disseminated sclerosis is inherited, which, however, is connected somehow with a more general neuropathic constitution. The latter is unspecific aud occurs in various nervous diseases".

The work of *Curtius* stimulated the interest in relevant problems and a number of instances of the familial occurrence of multiple sclerosis were published. *Mackay* (1950) made a careful scrutiny of the literature and found 84 families—5 of which he himself had observed—with two or more cases of multiple sclerosis, altogether 188 cases; he excluded all those which were inadequately described. He concluded from his studies that there is a familial constitutional tendency—a vulnerability—to the disease. "This vulnerability, possibly non-essential and non-specific, is subclinical, and *per se* inadequate to produce the disease."

Pratt et al. (1951) found in the literature 184 families—who in their opinion were "acceptable"—of which more than one member had multiple sclerosis. In their own case series comprising 310 patients at the Middlesex Hospital there were 20 who had one or more relatives with the disease—an incidence of 6.5 per cent. (In 15 cases the relatives were parents or siblings, and in 5 cases more distant relatives). The risk of relatives to persons with multiple sclerosis contracting the disease would, according to the authors' own calculations, be 13–18 times greater than for the general population. The authors concluded that there is in multiple sclerosis a genetic factor that may allow the aetiological factor to act more readily.

Other authors, however, consider that the genetic factors play an insignificant role. *Thums* (1939) found 14 monozygotic pairs in a series of 50 sets of twins with multiple sclerosis. All 14 were discordant with respect to multiple sclerosis and *Thums* concludes that the disease is in the main an environmental one. In a larger series of 20 sets of identical twins he found, however, one concordant pair (1949). *Thums'* work has been criticized by *Mackay* (1950) on the grounds that no proof is offered that the twins were monozygotic and that several of the pairs were still of an age when symptoms might yet appear. *Kurland* (1952 a) pointed out the difficulties in differentiating between multiple sclerosis and hereditary degenerative nervous diseases; from a critical study of the literature he inferred that heredity factors seem to be of little significance to the aetiology of multiple sclerosis.

Müller (1953), who conducted a study of a large number of patients, disputed the importance of genetic factors. Of 750 multiple sclerosis patients (probands) he personally examined the 569 who were still alive and visited two or more close relations of those who died before the examination. Of these 750 probands 27 (3.6 per cent) had some near relative who was suffering from multiple sclerosis. The incidence of multiple sclerosis in the whole group of observed relatives over 9 years was 0.6 ± 0.11 per cent. *Müller* made a critical scrutiny of the morbidity rates for multiple sclerosis from various sources. He found the data based on official statistics on causes of death to be extremely unreliable. Other investigators worked with data from hospitals and practising physicians. *Ibsen* (1950) and *Kurland* (1952) with this method found an incidence of 0.04 per cent and 0.05 per cent in various regions of the United States and Canada. However, *Müller* considered that the figure is in fact larger, as it is likely that many cases in an early stage of the disease are overlooked. In a study of the relatives of a group of patients performed by a neurologist it would on the other hand seem rather unlikely that any cases would be overlooked. *Müller* considered, therefore, that the figure he found from his series could not be compared directly with the data on morbidity obtained by other workers. A further difficulty in making a direct comparison is that the age distribution in the group of relatives is different from that of the general population, and that the chance of contracting multiple sclerosis varies with age. *Müller* accordingly concluded that a morbidity of 0.6 ± 0.11 per cent among the relatives of the patients cannot be considered definitely higher than that which may be expected in an average population although this might well be the case. He also pointed out the very low degree of manifestation—less than 5 and 10 per cent, respectively—that would have to obtain if it were supposed that there was a dominant or recessive hereditary transmission. He quoted *Alström* (1950), who asserted that a genetic explanation of a disease should not be advanced if it was necessary to count with an inhibition of manifestation above 90 per cent. *Müller* finally pointed out that the lower percentage (3.6 per cent) of patients with relatives having the disease in his series was not indicative that the genetic factors, in the wider sense of the term, are of no significance. It is possible that there is a genetically determined reduction in resistance to the disease as has been supposed to be the case in, for example, tuberculosis.

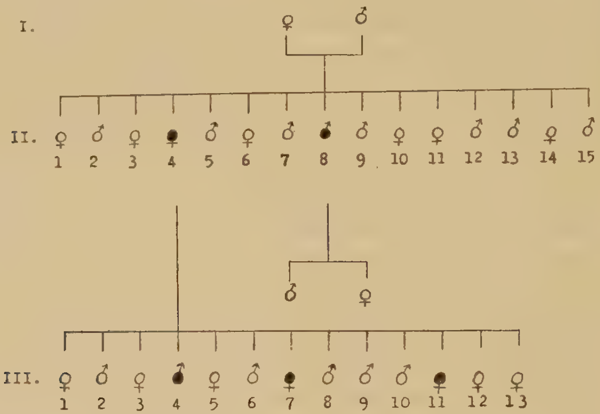
Millar & Allison (1954) have recently published the results of a well-planned and meticulously performed investigation in Northern Ireland into the occurrence of multiple sclerosis in the whole population (the prevalence) and in families. While the study was in progress, a census was made, as a consequence of which the authors had access to new population figures. In this investigation the majority of the sources of error that apply to earlier calculations of the morbidity were, as far as can be judged, eliminated. These workers studied 668 families in 44 of which they found more than one member suffering from multiple sclerosis—giving a familial incidence of 6.58 per cent. This figure was compared with that of 6.5 found by *Pratt et al.* (1951) and 6 by *Campbell* (1952). The morbidity among the relatives was between 0.65 and 1.15 per cent in this series, which accords with the figure of 0.82 for the series of *Pratt et al.* and 0.9 for the series of *Curtius & Speers* (1937). The incidence among relatives was 5 to 15 times greater than for the whole population of Northern Ireland. *Millar & Allison* observe by way of summary:

"We feel confident in stating that there is a familial incidence in this disease. . . . The figures, although conclusive, are small, and the familial factor cannot be the only one; like many other diseases, there are both genetic and environmental factors."

They also collate the reported instances of identical twins of which one or both members suffered from the disease. Of 26 sets of twins 8 (30.8 per cent) were concordant, a fact that the authors consider as bearing out the supposition that there is a genetic factor in multiple sclerosis but that this is not the only factor acting.

Müller (1953) pointed to the small number of reported instances of more than two cases of multiple sclerosis in the same family. In a scrutiny of the literature on the basis of diagnostic criteria indicated by *Mackay* (1950) and *Pratt et al.* (1951) the author found 33 families with 3 cases of multiple sclerosis, 5 families with 4 members affected (14, 20, 21, 22, 23) and one family with 5 (*Pratt et al.*). In addition there is a number of cases that are inadequately described; *Schaltenbrand* (1943) for example, mentions a family with 5 cases in three generations, *Duzière et al.* (1951) a family with 6 cases (of which only three were described in detail) and *Robinson & Robinson* (1929) a family with 8 cases (of which 4 are described).

In addition to these families with large numbers of cases of multiple sclerosis mention may be made of one with 5 cases in two generations: two sisters, one brother, their mother and uncle[1].



Case II: 4. H.S. ♀, born 1882. Previous history unknown. At the age of 38 years there was periodic loss of power in first one and then both legs. Probably did not have any paraesthesia or temporary impairment of vision. After periods of improvement the paralysis of the legs gradually increased and the patient had difficulty in keeping her balance; involuntary tremor and difficulty in writing. She was examined in June, 1924, by Dr. Gustaf Hultén, Vrigstad: spastic paraesis in both legs, Babinski reflex present bilat.; remitted with diagnosis of multiple sclerosis.

The patient was tended at Sävsjö hospital from 14.6. to 21.8. 1924; multiple sclerosis was diagnosed. No case history or status was noted. It appears from the temperature curve that a lumbar puncture was performed and the W.R. in the cerebrospinal fluid was negative. The nurse in charge of the patient recalled that the patient had very slurred speech and incontinence of urine and faeces. She was subsequently tended at home where she died of some complication in September of the same year. No autopsy was performed.

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[1] Thanks are expressed to Prof. M. Fog, M.D., the University Hospital, Copenhagen, Dr. W. Örn, the Military Hospital, Eksjö, Dr. O. Nordenfelt, the Central Hospital, Jönköping, Dr. P. B. Edén, Sävsjö, and Dr. G. Hultén, Vrigstad, for their permission to reproduce data from the case reports.

Case II: 8. K.S. ♂, born 1890. As a child he suffered from morbilli and parotitis. At the age of 32 rapid attacks of dizziness with a tendency to fall to the right, lasting a short time and occurring at intervals of weeks or months. These attacks disappeared after 2 to 3 years. 1927 "inflammation" of the left ear (no secretion); subsequent reduced hearing on the left side.

About 1933 weakness in the right calf and ankle, increasing gradually. About 1937 weakness in right arm and clumsiness of the right hand. Tended at the military hospital in Eksjö from 17.11. to 12.12. 1937; diagnosis: multiple sclerosis. *Status included:* speech somewhat indistinct; reduced power in the right leg and slight reduction in the left. Romberg's sign uncertain, possibly a tendency to fall to the right. Abdominal reflexes absent, marked reflexes in the lower extremities and Babinski reflex present. W.R. in blood and C.S.F. negative. Normal C.S.F. Mastix negative.

Subsequently his symptoms progressed slowly without any definite remission and led to practically complete paralysis of the right leg and arm. 1951 the patient fractured the right thigh. Admitted for this to the Hospital for chronic diseases in Vetlanda 30.11.51 to 30.5.52. Diagnosis: multiple sclerosis + fracture of right femur. Status on arrival included: "Typical multiple sclerosis with nystagmus, scanning speech, poor sense of balance, Babinski reflex positive, marked reflexes."

After about 1952 there was increasing weakness also in the left leg. Paraesthesia in the extremities on the right side; no aching. Gradually increasing loss of sensibility of right hand and leg.

Tended at the Central Epidemic Hospital in Jönköping from 9.2. to 12.2.55. Diagnosis: multiple sclerosis. *Status included:* vision and fundus normal. Hearing somewhat reduced bilaterally. No nystagmus. Considerable paresis of the whole of the right arm, practically complete in both legs with a tendency to adductor contractions. Superficial reduction of sensation on the dorsal side of the right hand and the whole of the right leg. Sense of vibration absent on the right hand, reduced for both legs, the right more than the left. Intention tremor and adiadochokinesis on the right. Romberg's sign pos. Spastic, ataxic gait. Abdominal reflexes absent. Muscle reflexes normal in the upper extremities, exaggerated in lower extremities. Babinski reflex present bilat. Ankle clonus on right. Trömner's reflex present in the right hand. In C.S.F.: Pandy's test trace, Nonne's test negative. Cells: 2 per 3.2 cu.mm. Total protein 45 mg per cent. Mastix negative. W.R. negative.

Case III: 4. R.S. ♂, born 1907. At 14 years of age the patient suffered for short period from an undiagnosed illness with temperature, headache, vomiting, disorientation. In 1929, at 22 years of age, there was a progressive impairment of vision. On examination at the Serafimer Hospital ophthalmic clinic in 1929 the acuity of vision was less than 0.1 D bilat. There was possibly some temporal pallor of both discs. Diagnosis: multiple sclerosis. Some difficulty in walking on account of weakness of the legs. Tended at Jönköping Hospital from 3.8. to 3.11.29. Diagnosis: multiple sclerosis. *Status included:* somewhat euphoric state of mind. Scanning speech. Vision on both sides 2/50. Relative central colour scotoma. Rather far advanced "genuine" atrophy of the optic nerve. No nystagmus. Intention tremor.

Romberg's sign positive. Gait somewhat spastic, and unsteady. Abdominal reflexes: left absent, right upper and central present, lower right absent. Babinski reflex present bilat. C.S.F.: 7 poly-morpho-nuclear cells, 300 erythrocytes. Pandy and Nonne tests indicated traces of protein. W.R. in C.S.F. and blood negative. Condition improved somewhat, but deteriorated the following year. Admitted again to the Jönköping Hospital 3.3. to 4.4.1930. Diagnosis: multiple sclerosis. *Status included:* scanning speech. Vision: finger-counting at 10 ft., pallor of both discs, especially temporally. Slight nystagmus on right lateral gaze. Intention tremor. Waddling, spastic, staggering gait. Romberg positive. Abdominal reflexes absent. Babinski reflex present bilaterally.

After a period of some improvement there was considerable deterioration. Admitted for the third time to the same hospital 7.8. to 22.11.31. Diagnosis: multiple sclerosis. Paresis of both legs and marked ataxia in both arms, mostly the left, so that the patient could not eat without assistance. Patient transferred to hospital for chronic diseases, where he died of bronchitis in 1937. No autopsy.

Case III: 7. M.S. ♀, born 1915 (Information about the patient's previous history not available as she was resident in Denmark from 1925). At 15 years of age impairment of vision of both eyes. The following year there was difficulty in walking, with loss of power and control of the lower extremities. Tended at the Neurological Clinic of the University Hospital, Copenhagen, from 6.5. to 12.7.32. Diagnosis: multiple sclerosis.

Extracts from the case report: "Objective observation of flexion paresis in the hips. Deep reflexes increasing spastically with bilateral ankle clonus; Babinski reflex present bilaterally. Muscles hypertonic with slight spasticity. Peculiar deep excavation of both optic discs; their boundaries sharp; condition of retina otherwise normal. No evident scotoma. Pupil and mobility of the eyes normal." No data on lumbar puncture.

According to the patient's doctor there was periodical improvement in the patient's condition during the first year; gradually increasing paralysis of both arms; pronounced tremor. Completely disabled. During the last years before the patient died—1948—the disease progressed steadily. No autopsy.

Case III: 11. B.C. ♀, born 1921. Previously in good health except for, about 1940, occasional aching in the legs at night-time.

Acutely ill on 11.11.54 with pricking sensation in right big toe, and after an hour or so in the left. This was followed by a sensation of numbness, spread over 4 or 5 days, from the lower part of the body upwards to the trunk. The patient had an impression of reduced cutaneous sensation on the legs, the ankle and knee joints feeling as if bandaged, the feet feeling clumsy. Muscular tremors on exertion. No paralysis. No symptoms in the upper extremities.

Admitted 17.11.54 to the Central Epidemic Hospital, Jönköping, for examination. Neurological symptoms: middle and lower abdominal reflexes absent bilaterally and a definite reduction of the sense of vibration in the lower extremities with a marked boundary at a level of L I–L II. The nervous status otherwise normal. No signs of retrobulbar neuritis. On arrival at the hospital the C.S.F. revealed 10 leucocytes per 3.2 cu.mm. Pandy ++, Nonne (+), total protein 57 mg per cent. Mastix 888742. W.R. in blood and C.S.F. negative.

Multiple sclerosis was diagnosed as probable. The treatment was with ACTH. The marked paraesthesia in the lower extremities disappeared after about 2 weeks while the sense of vibration did not improve. On discharge 11.12.54 all abdominal reflexes were absent; the nervous status was otherwise as on admission.

Admitted again to the Central Epidemic Hospital for control 12.1. to 14.1.55. The patient still had occasional prickling sensation and numbness and "electric shocks" in the feet and legs. In addition she had on occasions similar paraesthesia in the left hand and some distance up on the arm. Sometimes slight dizziness and uncertain balance. The nervous status was unchanged apart from a caudal displacement of the boundary of reduced pallesthetic sensibility, so that it was then at the level of the L IV–L V. C.S.F.: 6 leucocytes per 3.2 cu.mm., total protein 31 mg per cent. Mastix 888860. W.R. negative.

At another control on 23.3.55 the patient reported that she still had occasional paraesthesia in the lower extremities and the left arm, and for short periods a dull aching in both hip-joints. The nervous status was unchanged. C.S.F.: 14 leucocytes per 3.2 cu.mm. Mastix 677762.

DISCUSSION

The diagnosis of multiple sclerosis may often be extremely difficult, especially in the early stages. *Pohlen* (1942) analysed the correlation between the clinical and the pathological diagnosis, using data from 25,000 autopsies in New York and New Jersey. Of 33 cases diagnosed as multiple sclerosis only 23 could be verified on post-mortem examination. On the other hand, for 11 patients autopsy findings revealed multiple sclerosis that was not diagnosed during life. *Müller* (1949) in some extensive investigations could confirm only 950 of 1,850 original diagnoses of multiple sclerosis.

When considering the occurrence of multiple sclerosis in families the disease must be differentiated from other neurological disorders—and primarily from spino-cerebellar ataxia, including Friedrich's variant and other forms of spastic ataxia and paraplegia. *McAlpine et al.* (1955) in a recently published monograph on multiple sclerosis state that one of the most important criteria is that spino-cerebellar ataxia generally appears before the age of 20 years, while the onset of multiple sclerosis occurs before 20 years of age in less than 20 per cent of the cases. In the former diseases the onset is, moreover, generally extremely insidious and the progress is characteristically slow, while the onset symptom in multiple sclerosis may appear suddenly and then abate or disappear during the remissions that are typical of the disease. A characteristic trait in hereditary spino-cerebellar ataxia is said to be that the onset occurs at the same age for different members of the family (*Bell & Carmichael,* 1939), which is less often the case in familial multiple sclerosis. Paraesthesia and disturbances of superficial and deep sensibility, which are so common a feature of multiple sclerosis, are rare in hereditary ataxia (seen, however, in Friedrich's variant). Abdominal reflexes and sphincters remain unaffected in hereditary ataxias; these, moreover, also do not affect the general health as early in the course of the disease as multiple sclerosis. Impairment of the vision occurs in spino-cerebellar ataxia, but this is then progressive, in contrast to the case in multiple sclerosis, in which it is generally due to retrobulbar neuritis and is transitory. C. S. F. data may also be of value in the differential diagnosis; in the familial spinal ataxia the C. S. F. is normal, while in multiple sclerosis there is often an increase in the protein content and a positive colloid reaction. *Millar & Allison* (1954), however, quote, a number of cases with symptoms and objective findings that differ from those generally accepted; they maintain that a differential diagnosis between hereditary spastic ataxia and multiple sclerosis may be very difficult, if not impossible, on clinical grounds.

For the diagnosis of multiple sclerosis certain characteristics may be looked for. *Mackay* (1950) lists the following:

(1) Onset between 12 and 50 years of age.
(2) Dissemination of the lesions in space, including involvement of the pyramidal tracts, exaggerated tendon reflexes, weakened or absent abdominal reflexes, positive Babinski reaction, disturbances of cerebellar function, often with nystagmus, involvement of the dorsal columns, and impairment of vision.
(3) Remissions and exacerbations.
(4) General increase in disability.
(5) Absence of clinical and serological evidence of syphilis.
(6) Changes in colloid gold curve of the cerebrospinal fluid.

Mackay added that all these characteristics are seldom found in any one case.

The positive findings in the histories of the five cases reported are summarized below on the basis of the above criteria.

Case II: 4. Mother. Onset at 38 years with weakness in one leg. Spastic paresis in the legs, Babinski reflex present, disturbed sense of balance, intention tremor, slurred speech, sphincters disturbed. Remissions at first. Increasing disability. W.R. in C.S.F. negative.

Case II: 8. Uncle. Onset at 32 years of age with disturbance of balance. Spastic paresis in legs and right arm, increased muscle reflexes, normal C.S.F., abdominal reflexes absent, Babinski reflex present, ankle clonus; cutaneous sensibility reduced, ataxia, adiadochokinesis, nystagmus. Remission after onset. Increasing disability. W.R. negative in blood and C.S.F.

Case III: 4. Brother. Onset at 22 years of age with impairment of vision, spastic paraplegia, Babinski reflex present, abdominal reflexes absent, nystagmus, intention tremor, ataxia, Romberg's sign positive, scanning speech, temporal pallor of discs, central scotoma. Remissions. Increasing disability. W.R. negative in blood and C.S.F.

Case III: 7. Sister 1. Onset at 15 years of age with impaired visual acuity, spastic paraplegia, exaggerated deep reflexes, Babinski reflex present, ankle clonus, intention tremor. Remissions. Increasing disability.

Case III: 11. Sister 2. Onset at 33 years of age with paraesthesis in legs. Abdominal reflexes absent, reduction of sense of vibration in lower extremities, paraesthesia in legs and left hand and lower arm. Remissions. W.R. negative in blood and C.S.F. In C.S.F. increase in cell and protein positive Mastix reaction.

In all five cases the criteria for a definite diagnosis of multiple sclerosis may be considered as fulfilled and there would seem to be no reason for considering spino-cerebellar ataxia.

SUMMARY

1. A short survey of the literature on the subject is given, with more detailed references to the papers of *Müller* (1953) and *Millar & Allison*. The excellent studies of the latter would seem to point to the presence of genetic factors in the occurrence of multiple sclerosis.

2. Reports have been found of 33 families having 3 cases of multiple sclerosis among relatives, 5 families with 4 cases and one family with 5 cases. Another family with 5 cases is reported here comprising two sisters, one brother, their mother and uncle. Detailed clinical descriptions are given.

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THE ACTIVITY IN SITU OF 5'-NUCLEOTIDASE, PHOSPHOMONOESTERASE AND THIAMINE PYROPHOSPHATASE IN VITAMIN B_1 DEFICIENT BRAIN TISSUE

By

D. NAIDOO

Ochoa and *Peters* (1938) showed that Vitamin B_1 is nearly exclusively present in animal tissues as aneurin (thiamine) pyrophosphate. The vitamin is converted by the tissues into a pyrophosphatase and in this form it enables glucose metabolism to go beyond the pyruvate stage (*Banga, Ochoa* and *Peters,* 1939). *Green Strumpf* and *Zarudnaya* (1947) showed that aneurin pyrophosphate participates in other metabolic processes in nervous tissue. In the oxidation of pyruvate *Peters* and his colleagues (1939) found that free aneurin was more effective than aneurin pyrophosphate in stimulating the respiration of brain preparations from Vitamin B_1 deficient animals. A possible explanation of this finding was that the tissue was poorly permeable to aneurin pyrophosphate but more permeable to aneurin itself. This view presupposes some dephosphorylating mechanism whereby aneurin phosphate is degraded to free aneurin. Consequently, aneurin was able to pass the permeability barriers, become rephosphorylated and take part in metabolism as the coenzyme.

The dephosphorylation of aneurin pyrophosphate by brain tissue was observed by *Ochoa* (1939). *Westenbrink, Parve* and *Goudsmit* (1943) described an active phosphatase hydrolysing the phosphoric acid esters of aneurin. It was found that this enzyme successively removes two phosphate groups from the pyrophosphate so that at one stage aneurin orthophosphate is left as an intermediary before aneurin is finally released.

Naidoo and *Pratt* (1952) demonstrated the sites of hydrolysis of aneurin pyrophosphate in the rat brain and showed that the histological

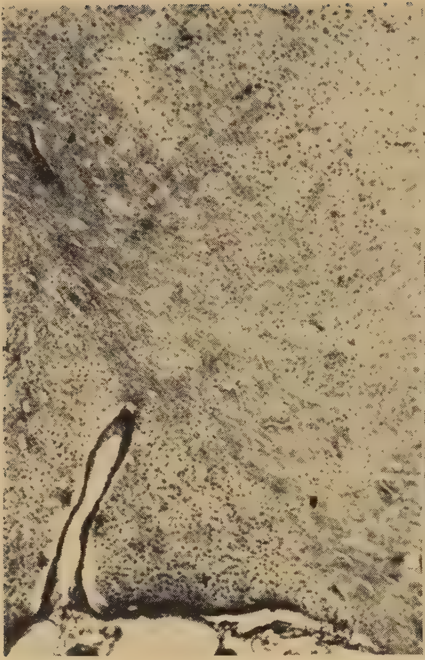

Fig. 1.

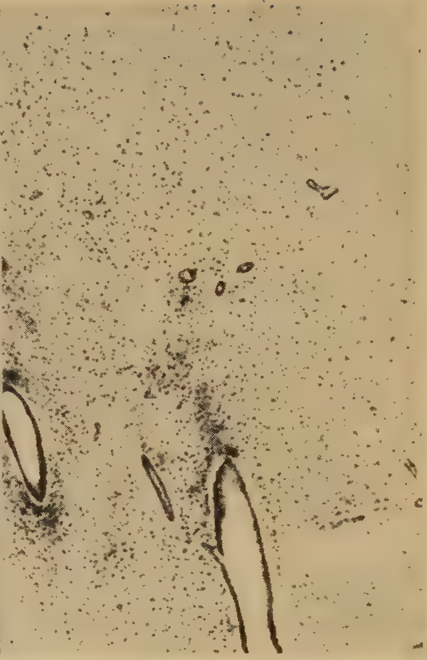

Fig. 2.

Fig. 1. Pretectal Brain. × 37.5. Normal. 5'-nucleotidase. Showing fibres and nuclei staining with equal intensity.

Fig. 2. Pretectal Brain. × 37.5. Aneurin deficient. 5'-nucleotidase. Nuclear staining appears more marked whereas fibres do not stain.

sites at which the activity can be localised and the biochemical conditions in which it can be demonstrated differ from those previously described by them when other phosphoric acid esters were used as substrates. They (*Naidoo* and *Pratt* 1953) identified some of the phosphatases situated in similar sites in brain tissue and came to the conclusion that the enzyme hydrolysing aneurin pyrophosphate and that hydrolysing glycerophosphate can be shown to be functionally distinguishable from each other. The behaviour of this enzyme in Vitamin B_1 deficient brain tissue therefore, promised to be of considerable interest.

In 1934 *Reis* described and later extended his description (1937–8, 1938–9, 1940, 1950, 1951) of an enzyme hydrolysing adenosinemonophosphate which was present in the brain. *Gulland* and *Jackson* (1938) also observed the presence of this enzyme, adenosinemonophosphatase or 5'-nucleotidase. Although no clear function can be ascribed to this enzyme *Naidoo* and *Pratt* found it to be located in the nerve fibres (1951) and also showed later (1954) that during maturation of

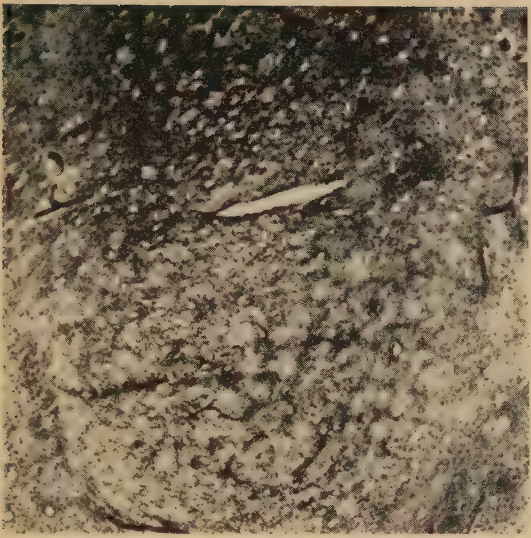

Fig. 3.
Nucleus Rotundus. × 37.5. Normal. 5'-nucleotidase. Showing fibres and nuclei staining with equal intensity.

the animal there was an increase in enzyme activity which was most rapid between 15 and 80 days of age in the albino rat. They found the increase to be greater than can be accounted for by the decreasing water content of the brain and that the enzyme seemed to arise in the nerve fibres a few days after birth. The rate of development of the 5'-nucleotidase closely paralled the rate of myelination in the rat.

During experimental work on Vitamin B_1 deficient chickens in connection with aneurin pyrophosphatase activity an attempt to locate 5'-nucleotidase showed that differences were to be seen between the normal and deficient brain in respect of the localisation of this enzyme. It is proposed therefore, to describe the changes seen in the activity of both aneurin pyrophosphatase and 5'-nucleotidase in the brains of Vitamin B_1 deficient chickens.

EXPERIMENTAL MATERIALS AND METHODS

Production of Deficiency:

Day-old Rhode Island Red cockerels obtained from an accredited commercial hatchery were housed in an electrically heated "Hover" Brooder. The temperature was set in the brooding chamber at 35° C and progressively reduced during the first three weeks to room temperature which was maintained at 22° C by thermostatically controlled

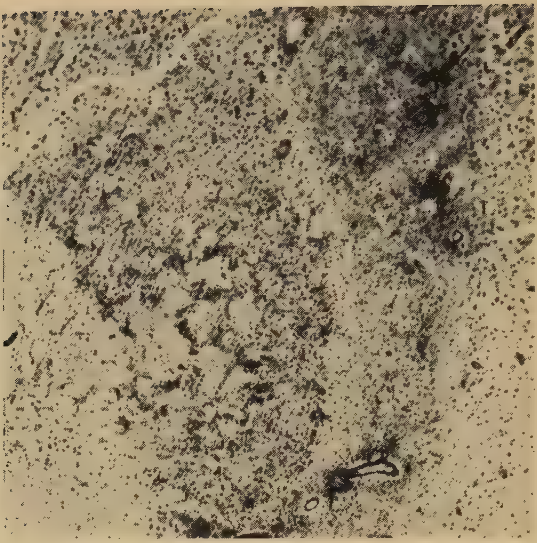

Fig. 4.

Nucleus Rotundus. × 37.5. Aneurin deficient. 5'-nucleotidase. Nuclear staining is increased but fibre staining is decreased.

steam heaters. The room was very well lit by daylight. The birds were kept on a wire mesh floor, the droppings falling on to metal trays so as to avoid possible coprophagia. The trays were cleaned out daily. Drinking water was provided and changed each 24 hours. A commercial chick mash obtained from Spillers Ltd., London, was allowed during the first three weeks without restriction.

At the end of the third week all weaklings and abnormal birds were rejected and the remainder were divided into two similar groups in respect of weight. The two groups were then placed in smaller adjacent cages. The tip of the upper beak was trimmed with veterinary scissors to prevent feather pecking. The commercial mash was withheld at this time and the birds were fed on synthetic diet which was mixed with water to a thick creamy consistency and introduced directly into the crop. The feeding was carried out twice daily at 9 and 17 hours approximately, with a metal syringe of a type normally used to apply ornamental sugar icing to cakes. The diet was prepared by grinding the mixture through a fine seive and mixing the resulting fine powder with water. 100 grm. of powdered diet to 100 ml. of water was used. A 12 cm. length of moderately stiff rubber tubing of external diameter 6 mm. and 3 mm. internal diameter was attached to the nozzle of the syringe, moistened with water and passed down the oesophagus into the crop. The bird was held in the left hand with the first two fingers placed upon the crop and the food mixture injected until the crop was palpably full. During the remainder of the day the birds were allowed to feed freely on a mixture of gelatin and cellulose powder.

Each bird in the control group housed in the adjacent cage received every second day an intramuscular injection containing 100 gamma of thiamine in saline. Each bird was weighed daily before the morning feed. Four sets of twelve birds each were used in this study.

The synthetic diet was a modification of that of *Coates, Kon* and *Shepheard* (1950) but omitting the thiamine.

COMPOSITION OF THE DIET

Dextrin	1200 g.
Casein (B.D.H.) (Vitamin free)	360 g.
Mixed Salts (Hegsted, Mills, Elvehjem and Hart)	100 g.
$CaHPO_4$	20 g.
Cystine	6 g.
Inositol	2 g.
Sulphite treated liver extract	15 g.
Lard	100 g.
Cod Liver Oil	20 g.
Heptane extract from 60 gr. dried grass	
Choline chloride	3 g.
Riboflavin	12 mg.
Ca pantothenate	30 mg.
Pyridoxin	8 mg.
Nicotinamide	100 mg.
2-Methyl-1:4 Naphthaquinone	100 mg.

The solid constituents were first ground. The last six ingredients were dissolved in 25 ml. 90 % aqueous ethyl alcohol. The lard, cod liver oil, and grass extract were mixed together and added to a little extra dextrin before incorporation with the bulk of the solid constituents. The liver extract and the alcoholic solution of the vitamins were added to the mixture in a similar way.

Each bird received 35–50 g. daily of the diet mixture when forced feeding was started, that is, at 3 weeks of age. The birds given thiamine supplement continued to receive this quantity of diet daily throughout the experiment but birds not given thiamine received less of the diet mixture towards the end of the experiment, owing to delayed emptying of the crop. The birds were killed by guillotine when fully developed neuropathy supervened.

Histological Method

The brain was removed immediately after decapitation and coronal slices of the tectum and pretectal brain of less than 2 mm. thickness were frozen dried by the procedure described by *Naidoo* and *Pratt* (1951, 1952, 1953).

The frozen dried sections were dewaxed in petroleum ether (boiling range 80°–100°) for two minutes followed by two rinses in isopentane (boiling range 27°–31° C). Almost immediately after the removal of the slide with its mounted section from the isopetane the dewaxing agent evaporated leaving the paper white section dry on the slide. The slide was then thrust with a sharp movement of the fingers into the incubating media previously prepared and held in readiness at 37° C in an incubator. The media were prepared as follows:

Aneurin pyrophosphatase medium:

0.1 M sodium maleate buffer (pH 7.1)	15.0 ml.
0.005 M solution aneurin pyrophosphate	3.0 ml.
0.1 M magnesium chloride	6.0 ml.
0.04 M lead acetate	0.75 ml.
Water (glass distilled) to	30.0 ml.

Adenosinemonophosphate medium:

0.1 M sodium succinate buffer (pH 6.5)	15.0 ml.
0.04 M lead acetate	1.5 ml.
0.01 M adenosine 5'-monophosphate	3.0 ml.
Water (glass distilled) to	30.0 ml.

Control of tissue activity in these media was obtained by omission of the phosphoric acid ester, by washing in running water, or dry heating to 100° C for 10 minutes or boiling for 1 minute, or by chemical pretreatment with trichloracetic acid and acetone. The use of enzyme inhibitors acting at relatively low concentrations were consistently employed with each batch of experimental material to be histochemically processed. Adjacent sections were used as controls and media containing:

Uranyl acetate	(10^{-3} M)
Lanthanum nitrate	(10^{-4} M)
Beryllium sulphate	(10^{3-} M) and
Cysteine	(10^{-3} M)

were employed to study the inhibitory effects of these substances when compared with the experimental tissues and to check the validity of the enzyme preparations.

Fig. 5.

× 60. Normal. 5'-nucleotidase. Lightly stained nuclei.

RESULTS

Nissl and myelin preparations of deficient brains did not show any histological abnormality. Sections of optic tectum incubated with glycerophosphate at pH 5.3 showed no differences of staining between the normal and the Vitamin B_1 deficient preparation at incubation periods up to 2 hours. In the alkaline range at pH 9.1 definite differences of activity and distribution were evident in the sections incubated for different intervals up to two hours. The deficient tectum showed an increase in the activity of the stratum opticum and the subjacent outer layers. In the inner layers nuclei of the neurones showed moderate staining. In the layers overlying the ependyma staining was deep. In the normal control no nuclei could be made out on microscopy and the outer layer immediately below the stratum opticum stained comparatively lightly. None of the zones of the tecta showed capillary endothelial staining. The neuropile between the inner layers was lighter in the deficient brain. In the sections incubated with thiamine pyrophosphate, the deepest stained layer was the stratum opticum in both control and experimental tissues. In the other layers staining of the nerve cell bodies was moderately deep in the normal, but considerably deeper

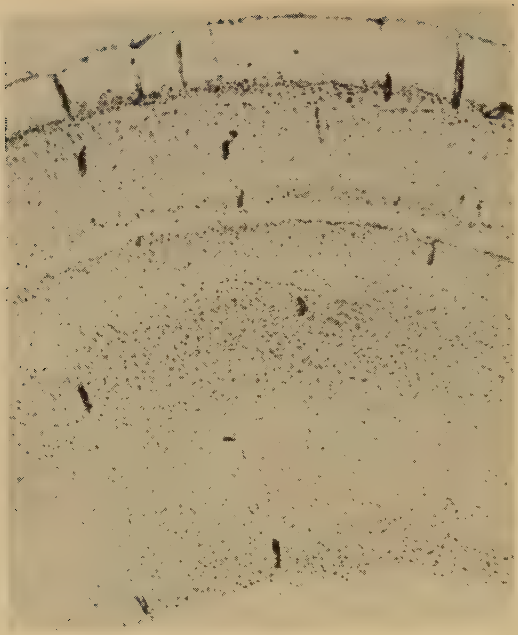

Fig. 6.

Optic Tectum. × 60. Aneurin deficient. 5'-nucleotidase. More deeply stained nuclei.

in the deficient bird. The neuropile in the deficient tectum was darker than that in the control.

The results following incubation with adenosine-monophosphate show that the deficient tectum and the pretectal brain the relationship between the intensity of activity of the fibres and the nuclei becomes altered. In the normal chicken both the fibres of the main bundles and the nuclei show activity with about equal intensity. In the Vitamin B_1 deficient chicken, however, the fibres fail to show activity but the nuclei appear under the microscope to have increased their activity. In the optic tectum fibre staining is negligible in the normal brain but nerve cells show moderate activity. In the experimental bird however activity in the cells is considerably increased.

DISCUSSION

The synthetic diet employed for this experiment makes possible controlled feeding of measured amounts of diet of known constitution which is adequate for normal growth when supplemented with thiamine.

In the last stages there was delayed emptying of the crop and a

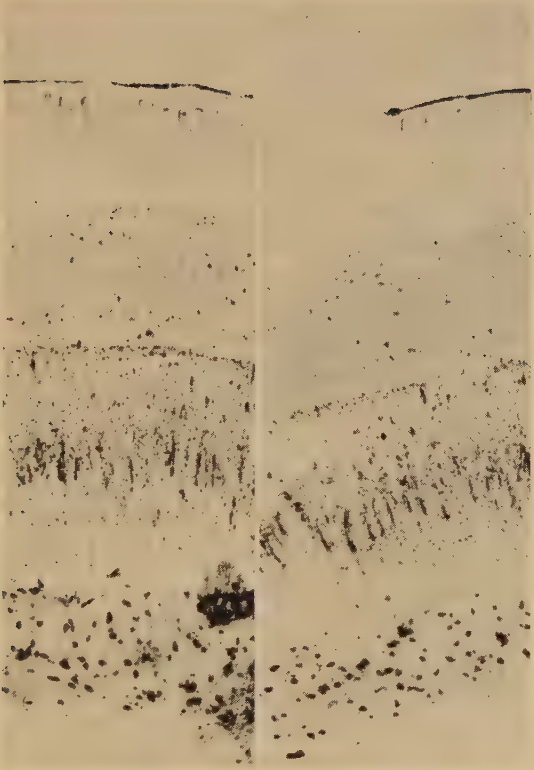

Fig. 7. *Fig. 8.*

Fig. 7. Optic Tectum. × 80. Normal. Acid phosphomonoesterase. Normal.
Fig. 8. Optic Tectum. × 80. Aneurin deficient. Acid monoesterase. No differences from normal.

condition resembling "sour crop" set in. This phenomenon is inseparable from the feeding of concentrated and consequently possibly irritating diets. The stasis in the crop usually became noticeable to palpation when the general neuropathy was advanced and a fully developed picture of peripheral neuritis was evident. The paralysis may have also involved the crop but it was at this stage that the animals were sacrified so that the question of under-nutrition does not seriously arise.

The results also show that chicken brain thiamine pyrophosphatase differs in some respects from the enzyme previously studied in the rat. *Naidoo* and *Pratt* (1953) observed that the rat brain enzyme showed high activity over a wider range of H^+ concentration, including pH 6.9 and 9.1, but the chicken enzyme only acts at a narrower range close to pH 8.4. The chicken brain enzyme, further, is activated only by Mg^{+2} whereas the rat thiamine pyrophosphatase can be activated either by

Ca^{+2} or Mg^{+2}. The activity of this enzyme tends to fall in birds, even those fed on thiamine supplemented diet suggesting that the level of enzyme activity may change with the maturation of the nervous system, (*Naidoo* and *Pratt,* 1955). There is a consistent increase in thiamine pyrophosphatase activity and in alkaline phosphatase activity but acid phosphatase shows no change. This finding is in keeping with the earlier biochemical observations by *Naidoo et al.* (1955). *Shimizu, Handa, Handa* and *Kumamoto* found (1950) a fall in acid glycerophosphatase activity but the finding cannot be confirmed by these results or by the quantitative results (*Naidoo* and *Pratt* 1935) but the change in the alkaline phosphatase activity is in full agreement with *Shimizu* and his colleagues. In connection with the acid phosphatase finding, it should be noted that the frozen dried chicken brain shows low acid phosphatase activity unlike the acetone fixed pigeon brain used in *Shimizu*'s work. This disagreement over the phosphomonoesterase in the acid range may be due to the probability that brain acid phosphatase activity may represent more than one enzyme (*Lowry et al.* 1954).

Matsukawa and *Yurugi* showed that thiamine pyrophosphate undergoes a series of reversible and irreversible changes in alkaline solution. It is possible, therefore, that if breakdown products accumulate during incubation they may form a substrate for alkaline phosphatase action. This would presuppose long incubation periods and notwithstanding this only a small proportion of the increase of enzyme activity observed can be accounted for in this manner.

It may be held that the enzyme changes are a sequel to the tissue changes and that the process is degenerative. Careful histological examination showed no haemorrhages in the tecta or periventricular grey matter. Neither was there evidence of a glio-mesodermal reaction. By the ordinary staining techniques no histopathological changes of any type could be seen.

It is difficult to explain why enzyme activity should increase rather than decrease. The observation that one of the enzymes studied, namely, acid phosphatase should remain unchanged in a tissue where other associated enzyme activity is rising cannot be readily understood particularly as *Bodin* and *Mellors* have shown this enzyme to increase its activity after axon section. *Naidoo* and *Pratt* (1954) found that neither alkaline phosphatase nor thiamine pyrophosphatase undergo rapid changes post mortem and in the event of tissue ceasing to be metabolically active the possibilities are that there would be no change in enzyme level or there would be a fall. It seems, therefore, likely that the changes seen in enzyme activity are due to altered metabolism.

The significance of the consistent finding of failure of fibre activity when adenosine monophosphate is used as a substrate in the thiamine deficient brain is also not clear. That the finding can also be substantiated by biochemical estimations was shown by *Naidoo* and *Pratt* (1954). It is possible that during the period of growth in the chicken the activity of the enzyme increase as it does in the rat (*Naidoo* and *Pratt*, 1954) and consequently the failure of fibres to show activity in thiamine deficiency adds to the validity of the finding.

SUMMARY

1. The activity of thiamine pyrophosphatase, acid and alkaline phosphomonoesterases and 5'-nucleotidase have been studied in the thiamine deficient chicken brain.
2. Mg^{+2} activated thiamine pyrophosphatase at pH 8.4 consistently increases in thiamine deficient chicken brain tissue.
3. Alkaline phosphomonoesterase shows consistent increased activity but acid phosphomonoesterase shows no changes in activity.
4. 5'-nucleotidase activity is not seen in nerve fibres in the deficient brain whereas the fibres are active in the normal animal. The nerve cell nuclei and glial cells appear to show increased activity in the deficient brain when compared with the normal.
5. The possible significance of these results is discussed.

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(FROM THE NØRRE HOSPITAL. CHIEF: PROFESSOR E. JARLØV, M.D.; AND THE NEUROLOGICAL DEPARTMENT OF THE MUNICIPAL HOSPITAL. CHIEF: DR. K. KRABBE, M.D.)

THE SIGNIFICANCE OF LIVER FUNCTION IN THE FORMATION OF FIBRINOGEN IN MULTIPLE SCLEROSIS

By

IB PERSSON

INTRODUCTION

Several theories have been put forward as to the etiology of multiple sclerosis, though it has not been possible finally to confirm any of them. In recent years interest has especially been concentrated on the theory advanced by *Putnam* (1936, 1937, 1937). On the basis of pathological-anatomical and experimental investigations he concluded that in multiple sclerosis vascular destruction or thrombosis formation occurred in the small veins in the central nervous system, thus initiating the formation of the characteristic plaques. It has not, however, been possible to maintain this vascular hypothesis in its original form. *Broman* (1949) and *Haarr* (1949), among others, in the course of thorough investigations have been unable to demonstrate coagulation thrombi in plaques. On the other hand *Fog* (1948) showed that the plaques found in the spinal medulla in this disease are connected with the veins.

Even if it has not been possible to demonstrate coagulation thrombi in plaques in multiple sclerosis, it must, however, be emphasized that in human pathology thrombi cannot be identified with coagulation thrombi, since the blood platelets alone are able to agglutinate and block the vessels, thus causing infarction (*Copley* and *Houlihan* (1947), *Hirsch, Favre-Gilly,* and *Dameshek* (1950), *Singer, Bornstein* and *Wile* (1947)).

Earlier investigations (*Persson,* 1952) have shown that in relation to this disease certain factors may be demonstrated which seem likely to facilitate the thrombus formation. Thus, if the content of fibrinogen and globulin in plasma is increased, the electric charge of the thrombocytes is reduced, which might further the thrombus formation

(*Roskam,* 1926). In multiple sclerosis the plasma fibrinogen just seems to be abnormally high in several cases (*Persson,* 1952), and so this might facilitate thrombus formation. *Putnam* (1941) has, similarly, carried out investigations concerning the plasma fibrinogen in multiple sclerosis, and he found an increase in some cases and a reduction in others. His results, however, are stated in relation to a normal value which has not been defined, so that a close evaluation cannot be made, and furthermore the low values are stated as especially pertaining to patients who had recently undergone acute exacerbations. This last finding agrees with the results of investigations made by the author (*Persson,* 1955).

It followed from this that an investigation into the site of the formation of fibrinogen seemed to be of value in order to determine whether the increased fibrin which may occur in multiple sclerosis can possibly be due to an increased formation of fibrinogen. Agreement has not been reached, though, as to the site of the formation of fibrinogen. However, according to the predominant theory (*Jacoby,* 1900) fibrinogen is produced solely in the liver, as it is not re-formed when the liver is cut off from the circulation, and it is likewise pointed out that the formation of fibrinogen is hampered by the substances which cause destruction of the liver or interfere with its function. Other investigations, however, seem to show that fibrinogen formation may also occur in the spleen or in the bone marrow (*Kisch,* 1923). An investigation of the bone marrow in multiple sclerosis (*Persson,* 1952), on the other hand, did not indicate any changes in it.

Other observations concerning multiple sclerosis also make an investigation into the functions of the liver desirable. Thus it was demonstrated by *Fog* (1951) that the prothrombin content of the blood was very low during the treatment of this disease with dicoumarin, the same as is found, for instance, in diseases of the liver.

In some diseases both the brain and the liver are found to be attacked, e.g. Wilson's hepato-lenticular degeneration. On the basis of this observation further investigations into the metabolism of the liver in neurological diseases have been carried out, including cases of multiple sclerosis, but these investigations have given variable results.

Brickner (1930) claims having demonstrated that serum from patients suffering from multiple sclerosis has a myelinolytic effect. Experiments by means of ligation of the bile duct in dogs showed, however, that serum from such animals also has a strong myelinolytic effect. On the basis of these experiments *Weil* and *Cleveland* (1932) advanced the hypothesis that in multiple sclerosis a myelotoxic substance is found, which is either formed in the liver, or which the latter is no longer able to detoxify.

Consequently a closer investigation into the functions of the liver in multiple sclerosis was found to be of importance. So, on the basis of an investigation into several of the functions of the liver it was attempted to make it possible to assess whether a raised fibrin content in the blood might be considered to be the cause of increased formation of fibrinogen in the liver.

CLINICAL MATERIAL

The investigations comprised 40 patients suffering from multiple sclerosis. Since the values for some of the tests of function varied according to the age of the patient, the patients were so chosen that their ages were between 21 and 46 years. The investigations concerned an equal number of men and women. The disease had been present for between 2 and 24 years—on an average for 12 years. In all the patients the course of the disease was chronic and progressive, and in none of the cases was it acute.

Conditions of Experiment and Methods of Estimation.

Estimations were made of quinine-resistant lipases (*Rona,* 1926), basic serum phosphatases (*Buch* and *Buch,* 1939), serum citric acid (*Thunberg,* 1929), prothrombin time (*Larsen* and *Plum,* 1941), urine urobilin (*Marcussen* and *Hansen,* 1918), urine urobilinogen (*Watson,* 1937), serum bilirubin (*Malloy* and *Evelyn,* 1937), icterus index (*Meulengracht,* 1921), the proteins (*Henriques* and *Klausen,* 1932), thymol reaction (*Shank* and *Hoagland,* 1946), Takata-Ara reaction (*Jezler,* 1929). Moreover a galactose test (*Bauer,* 1906) was performed on 15 patients. In each individual patient all blood tests were taken simultaneously and after a 15 hour fast, and in all at the same time of day.

Results of Experiments.

The results found are shown in the tables. Table 1 shows the number of cases in which values were found which are outside the limits fixed for the normal. On the other hand no attempt was made to show the mean and standard deviation, since that, as mentioned by *Wootton, King,* and *Smith* (1951), can only be done in cases where the experimental results lie close to the symmetrically "normal" form, which is only the case in some of the liver function tests.

TABLE 1

Liver function tests in 40 patients suffering from multiple sclerosis (galactose test in 15 patients only).

Test, unit of measurement, and normal value	No. of abnormal results
Quinine-resistant lipases (no. of drops below 7)	4
Basic serum phosphatases (Buch units, 2.0–9.4)	3
Serum citric acid (17–27 μg/ml.)	12
Prothrombin time (20–30 sec.)	0
Urine urobilin (positive in dilution 1/10)	4
Urine urobilinogen (0)	0
Serum bilirubin (0.1–1.2 mg%)	5
Icteric index (below 7)	4
Total protein (♀ 5.6–8.2 %: ♂ 6.3–8.1 %)	3
Albumin (♀ 3.5–5.5 %: ♂ 3.9–5.4 %)	7
Globulin (♀ 1.6–3.2 %: ♂ 1.7–3.2 %)	11
Relative globulin fraction (♀ 25–44: ♂ 24–43)	12
Thymol reaction (0–4 MacLagan units)	3
Takata-Ara reaction (negative)	0
Galactose test (0–3 gm.)	(0 out of 15)

TABLE 2

Abnormal liver function tests found in 40 patients suffering from multiple sclerosis.

Test	Values obtained
Quinine resistant lipases	♀ 14, 9: ♂ 8, 11
Basic serum phosphatases (raised)	♀ 10.6, 9.6: ♂ 9.9
Serum citric acid (raised)	♀ 28.8, 29.2, 30.2, 28.3,: ♂ 28.8, 28.0, 28.6, 30.1, 27.9, 28.4, 27.1, 31.5
Urine urobilin	Positive in a dilution of 1/20 in 4 patients
Serum bilirubin	♀ 2.14, 1.34, 1.40: ♂ 1.50, 1.81
Icteric index	♀ 10, 7: ♂ 7, 9
Total protein (reduced)	♂ 6.1, 5.5, 6.1
Albumin (reduced)	♀ 2.3, 3.3, 2.1: ♂ 3.7, 3.5, 2.9,
Albumin (raised)	♂ 5.6
Globulin (raised)	♀ 3.6, 3.4, 3.3, 4.0: ♂ 3.3, 4.5, 3.3, 3.4. 3.5
Globulin (reduced)	♀ 1.4: ♂ 1.5
Relative globulin fraction (raised)	♀ 61, 51, 60, 54: ♂ 44, 49, 61, 49, 45
Relative globulin fraction (reduced)	♀ 22: ♂ 22, 23
Thymol reaction	♀ 5.0: ♂ 4.7, 5.2

DISCUSSION

The investigations into several of the functions of the liver described above do not seem to indicate any grave damage of the liver in multiple sclerosis; for with very few exceptions all the results of the tests were within the limits of the normal. In 12 out of the 40 patients, however, the values for the serum citric acid were found to be on the limit of the normal, and in a few patients there was, in addition, a raised basic serum phosphatase, which might be taken to indicate a mild parenchymatous liver disease (*Buch*, 1942). A few months before these investigations were carried out one of the patients had suffered from hepatitis, but the course of this complaint conformed in every respect to epidemic hepatitis in any other patient. Consequently it may reasonably be assumed that this was nothing but a coincidence, and there was no indication that the course of hepatitis was different in a case of multiple sclerosis from what may otherwise be observed.

In some respects there is an essential deviation of these results from those of previous investigations as carried out, among others, by *Haug* (1934), who demonstrated a positive galactose test in half of the patients suffering from multiple sclerosis. In their investigations *Faust* (1953) and *Faust, Gros, Kirnberger* and *Bisser* (1953) found that the Takata-Ara and galactose tests were positive in up to 40 % of the cases, and especially the thymol tests were often positive, viz. in up to 70 % of the cases. With a larger series *Geinitz, Schild,* and *Schrader* (1954) found that the thymol tests were positive in 42 %, while the remainder of the above-mentioned tests only exceptionally showed abnormal values.

In investigating one or more of the functions of the liver, other authors, however, have found values which differ from those hitherto quoted. Thus *Jones, Jones* and *Bunch* (1950) found the serum bilirubin and the alkaline phosphatase to be normal, whereas the serum proteins were often lower than in normal persons, though they did not consider this difference to be significant. On the other hand *Swank, Franklin,* and *Quastel* (1951) found that the plasma proteins showed abnormal values during the active phases of the disease. *Bagni* and *Andreani* (1950) found slightly positive thymol values in about 25 % of the patients, and higher values were only exceptionally demonstrated, while raised values for serum bilirubin were found in about 20 % of the cases. *Fog* (1951) could only rarely demonstrate abnormal values. *Dekaban, Brodrick,* and *Waugh* (1952) found that a raised serum bilirubin only exceptionally occurred. *Dobin* and *Switzer* (1954), in their investigations into the functions of the liver in 58 patients suffering from multiple sclerosis, found that the liver function tests did not show any significant abnormalities.

The reasons for the differences in the results of experiments may partly be considered to be due to the fact that some of the above-mentioned earlier investigations concerned few patients, and partly the clinical material may be thought to have been differently composed. Moreover, different methods of investigation have been applied. In connection with nearly all the investigations we lack some indication regarding the limits within which values are said to be normal. Finally, experiments have shown that the identical method of investigation of identical samples gives different results when carried out in different laboratories (*Wootton, King,* and *Smith,* 1951).

As previous investigations (*Persson,* 1952) seemed to indicate that the fibrinogen content in plasma in multiple sclerosis remains at a higher level than normal, while it has been shown, on the other hand, that the formation of fibrinogen is interfered with by substances which cause liver damage (*Drury* and *McMaster* (1929), *Foster* and *Whipple* (1922), *Meek* (1912), it might be expected in advance that no sign of serious liver damage would be noticed, as the fibrinogen formation may also be considered a liver function test. It should be stressed, however, that some of the liver function tests may be normal, while other tests on the same patient may show abnormal values. For this reason an examination of several domains of the functions of the liver has been attempted in the investigations described here. Consequently it cannot be supposed that the low prothrombin concentration of the blood in multiple sclerosis during dicoumarin treatment as described by *Fog* (1951) should be due to a disease of the liver. Nor did he find this indicated in his investigations.

Subsequently the above-mentioned investigations seem to point to the possibility of the periodically raised plasma fibrinogen in multiple sclerosis being due to a raised production in the liver. It then becomes a question of assessing the importance of a raised production of fibrinogen in relation to the pathogenesis of the disease, as it is known that, among other things, an increased fibrinogen content in plasma occurs at thrombotic conditions (*Schulz,* 1953), and, as mentioned plaques might be supposed to arise in this manner. With regards to the evaluation of the importance of an increased production of fibrinogen in the liver for the pathogenesis of the disease, some previous investigations prove of use. Among other things it has been demonstrated that progression of the disease seems to be accompanied by a raised fibrinogen content (*Persson,* 1953), but it was also found that such a rise might occur without simultaneous aggravation of the disease. The fact that a periodically raised plasma fibrinogen was demonstrated without clinical signs of new plaques might either be due to possible thrombi being located in "silent zones", or to these thrombi having been too small to cause symptoms. The most likely solution is probably that the increased fibrinogen content has not caused thrombus formation, and that the actual provoking factor in the formation of thrombi has been lacking. The investigations also showed the sedimentation rate to be highly independent of the serum fibrinogen (*Persson,* 1952), which may mean that changes in other factors, among others the remaining serum proteins, are of some consequence. Moreover, it has been shown in other investigations that not only in multiple sclerosis, but also in other chronic neurological diseases there seems to be an increased fibrinogen content in plasma (*Persson,* 1952), without the observation being made of an increased tendency towards formation of thrombi in these other neurological diseases.

It then follows that the increased plasma fibrinogen content in multiple sclerosis can hardly be considered the provoking factor in the formation of thrombi, which maybe causes the formation of plaques, but is better regarded as a phenomenon parallel to the actual cause of the disease. Consequently the liver cannot be thought to be of any specific importance, through an increased fibrinogen production, in the pathogenesis of multiple sclerosis.

SUMMARY

On the basis of pathological-anatomical and experimental investigations *Putnam* has advanced the theory that in multiple sclerosis thrombi were formed in the small veins of the central nervous system, through which formation of the characteristic plaques was supposed to occur. Later investigations have shown, however, that it is maybe not a matter of coagulation thrombi; but it is possible that the blood platelets alone can agglutinate, thus blocking the vessels and causing infarction.

In connection with multiple sclerosis factors have been demonstrated which may be considered likely to facilitate the thrombus formation, so that, among other things, the plasma fibrinogen is raised. As fibrinogen is made in the liver, examination of the functions of the liver seemed to be of value in this disease.

The investigations described in this article concerning several functions of the liver, however, did not point towards any serious liver damage. Thus nothing argued against the raised plasma fibrinogen

content in multiple sclerosis being due to an increased formation in the liver. However, the raised fibrinogen content can hardly be considered the actual cause of the formation of thrombi which maybe produce plaques, as, among other things, a rise in the fibrinogen content which is not accompanied by the formation of thrombi in the central nervous system may occur in other chronic diseases. Hence it follows that as far as increased fibrinogen formation is concerned the liver cannot be supposed to be of any specific importance for the pathogenesis in multiple sclerosis.

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ON THE ZONE OF PROVOCATION OF THE DEEP MUSCLE REFLEXES

By

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To Professor *G. H. Monrad-Krohn,* deep and cordial hommage on his universitary anniversary.

The examination of the deep muscle reflexes is a fundamental part of clinical examination of the nervous system, a matter presented in masterful and classical fashion by Prof. *G. H. Monrad-Krohn.*

The elementary anatomic and functional basis of these reflex responses is the stretch reflex. Numerous neurophysiologists (*Liddell* and *Sherrington* (1), *Denny-Brown* and *Liddell* (2), *Lloyd* (3), *Szentágothai* (4)) have described the nature of the stretch reflex, e.g. its bi-neuronal arc, the "myotatic unit" with its direct inhibition, etc.

Creed and coworkers (5) described the stretch reflex as "the resistance offered by a muscle in full connection with the nervous system". It might also be said that the stretch reflex is the response supplied by a muscle when it is stimulated through its sudden passive elongation. Therefore, the stretch reflex is likewise the reflex resistance that the muscle opposes to its being distended.

By applying this neurophysiological information in the clinic, some authors have endeavoured to modify certain erroneous concepts relative to the deep muscle reflexes, as well as to renew the terminology of them. The book of *Wartenberg* (6) and several papers by the present writer may be consulted (7–10).

We have insisted on the fact that the deep muscle reflexes of clinics are particular modalities of the stretch reflex provoked at will by the examiner. They may be defined as phasic proprioceptive reflexes pro-

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duced through muscular distension usually provoked by means of percussion at certain elective points.

In order to define the phasic reflex response thus provoked, it is of interest to know, first, which is the muscle supplying it, but it is also of interest to know the characteristics of the clinical process of provocation. In fact, the reflex and its clinical valuation depend upon a relation, that is, the relation existing between the condition of "reflex susceptibility" of the muscle that supplies the response to distension—with all the individual characteristics of this response in each specific case—and the manner of application of the provoking percussion—with its details of topography, rudeness, intensity, direction, etc. The former—the muscle—is the fundamental thing, but it is necessary to know also the latter—the clinical provocation—in order to be able to evaluate the reflex response, to give to it a just semeiological interpretation.

We want to insist here especially on the terminology relative to one of the circumstances of the method of clinical provocation of the deep muscle reflexes: The extension of the cutaneous surface on which the application of the clinical percussion is effective for the provocation of the reflex of a muscle or specific muscular group.

The term traditionally used is "reflexogenous zone" and jointly with it, that of "increase, enlargement, or extension of the reflexogenous zone".

Wartenberg (6) already pointed out the evident incorrectness of this terminology, although he does not suggest any other to take its place, which is of course necessary.

The present author, in a communication submitted at the inaugural meeting of the "Sociedad Española de Neurología" (Barcelona, December 19, 1949) (7), insisted on the fact that the only zone or point really "reflexogenous" (generator of the reflex) of the deep muscle reflexes, is the receptor afferent of traction. The zone of application of the clinical stimulation does not by any means deserve this title, since there does not in itself, nor in the immediately underlying structures, exist any nervous termination having an active participation in the genesis of the reflex.

When under certain conditions of deep muscle hyperreflexia, included among the semeiological manifestations of the spasticity, reference is usually made to "extension of the reflexogenous zone", it is desired to indicate only—or it should be desired to indicate only—that the area on which the application of the usual stimulation is effective in the clinical examination has been increased, a contingent and circumstantial area, in no way directly connected with the origin of the reflex being investigated; an area, as we see, that is variable in its extension, while, on the other hand, the afferents of traction, where the reflex response is initiated, continue to be the same.

In view of all the foregoing statements we already indicated at that time (1949 (7), for the first time, that it was necessary to look for an expression which would clearly indicate that what is increased, what is enlarged, what is extended in such cases, is something that refers only to the possibilities, to the procedure, of clinical production. It concerns, therefore, something connected with the method, with the circumstance of the clinical examination, and not something intrinsic, congenial, essential, of the reflex itself.

In fact, the really reflexogenous zone or points do not increase. It is a question of a series of afferent receptors of traction which do not undergo any change, any increase or decrease. What is increased is only the area of efficient application of the clinical procedure of indirect stimulation.

In view of all that has been stated above, we suggested (1949) (7) that this area be called *"zone of provocation"*. And to refer also to increase, enlargement, or extension of the "zone of provocation".

Our suggestion was so successful that it was taken up and fully accepted in the recent editions of two textbooks of extraordinary success, the classic textbook of *Monrad-Krohn* (11) and that of *Wartenberg* on reflexes (in the case of the latter, through the translators of the French edition, *Bonduelle* and *Hell*) (12). This acceptance is what has caused us to prepare a short article on this subject published in Spanish (13) as well as the present different one for Scandinavian and Anglo-Saxon readers.

Although in connection with the central subject of the present paper it is advisable to introduce some comments on the anatomic-functional connections of the neuromuscular receptor afferent to traction, it would not be proper in a systematic manner to review the physiopathology of the spastic conditions which bring about an increase or exaltation of the profound muscular reflexes, one of whose clinical manifestations is the said increase of their "zone of provocation".

In 1952, the present writer reviewed the physiopathology of spasticity (14), including this study in the monograph "Patologia General del Sistema Piramidal" (General Pathology of the Pyramidal System) (10). Looking for a bridge between the classic ideas and certain recent demonstrations and hypothesis, we have suggested the term "juxtapyramidal" for the inhibitory projection of the reflex of traction, which, along its descending course remains at least intimately associated with the direct cortico-spinal projection or pyramidal tract "in a strict sense". By including both in an ample or renewed view of the "pyramidal" system, we may in this manner continue maintaining the classic idea of spasticity belonging to the pyramidal syndrome, very convenient for clinical practice.

We shall add that the systematization carried out by the *Magoun* school of the physiopathology of spasticity (15) has been criticized by *G. Clark* (16), on the basis of his well-known criticism of the concept of suppressing areas, parallel to that made by *Sloan* and *Jasper* (17) and by *Kaada* (18), and of the discordant results of the experimental sections of the bulbar pyramids. In some of our previous writings we have also dealt with the hypothesis of *Denny-Brown* on spasticity (19, 20). Those of us interested in these important questions, look forward to the publication in detail by this author of the results obtained by him through the sole interruption of the bulbar pyramid.

In spite of the criticism of their conception of the problem as a whole, the description by *Magoun* and his collaborators of a ventromedian bulbar reticular "centre" inhibitory of the stretch reflex and of a diencephalic, mesencephalic, protuberantial and bulbar laterodorsal reticular "centre", facilitating the stretch reflex, must be considered a real contribution to the better knowledge of the physiopathology of spasticity.

On the other hand, the investigations of *Granit* and *Kaada* (21) have made it evident that the susceptibility of the afferent neuromuscular spindles of traction to the proper stimulation, is variable and depends upon the influences exercised by various structures of the central nervous system through the innervation of the intrafusal muscular fibres by the gamma efferents of Leksell.

Granit and *Kaada* have proved that the gamma efferent system is tonically activated from certain central areas, while at the same time it controls the tonic activity of the afferent muscular spindles. The inhibiting and facilitating reticular systems of *Magoun* would also exercise an important influence through the gamma efferents.

The anatomic-functional system constituted by the gamma efferents, the afferents of traction and the motoneurons is designated by the Scandinavian authors as the "external loop".

Eldred, Granit and *Merton* (22) have seen that the interruption of the gamma efferents leads to a sudden fall of the discharge frequency of the spindles. Even at a tension of 0 the spindles activated through the gamma efferents (intact spindles and de-afferented spindles) had a discharge frequency higher than those deprived of the gamma efferents, which proves the "tonic" action of the external loop.

From the preceding statements it may be understood that on increasing the frequency of the impulses received by the intrafusal fibres through the gamma efferents, it is possible that some neuromuscular spindles come into such a condition of activation that it makes them sensible to slight stimulation of muscular traction which formerly resulted in being subumbral. The result of this may be that on passing from normal conditions to spasticity, the same muscle may see an increase in the number of spindles that respond to a specific stimulation of traction.

But this increase in the number of receptors, concerned within the same muscle have only an indirect and contingent relation to the enlargement of the zone of provocation on which the method of clinical exploration is applied. It is only the latter zone—we repeat, the zone of provocation and not a reflexogenous zone—that which the clinician looks for and sees and that to which reference is made in his records.

We may add here that the experiments of *Terzuolo* and *Terzian* (23) carried out on decerebrate cats by intercollicular or supracollicular section show that the regulation of the postural tonus is not effected only at the expense of the stretch reflex, the strength of which becomes regulated to a large extent by the efferent gamma, but that there exists other central influences independent of this "peripheral" circuit. Indeed, these authors have verified that stimulation at low frequencies of the anterior lobe of the cerebellum determines an increase of the tonus at a de-afferented extremity which persists even after denervating the contralateral extremity, de-afferenting bilaterally the vestibular nucleus (or extirpating both labyrinths) and sectioning the first three cervical roots. Similar effects, although independent of the frequencies of stimulation, were obtained by stimulating the facilitating reticular formation of the brain stem.

Terzuolo and *Terzian* end by affirming that such results show that the muscular tonus is not exclusively myotatic in its origin, i.e. that it is not entirely dependent on the stretch reflex, not even as conceived in a wide sense; we mean, including in it the external loop initiated by the efferent gamma.

On the other hand, *Cohen* (24) has recently proved the presence of two different types of direct spinal arcs in the organization of stretch reflex. These two relatively independent reflex pathways would, by stimulation of the same stretch receptors, produce two types of qualitatively different reflex responses: (a) a low threshold type, limited to an actually stretched strip of muscle ("strip response" or response of fine localization) and (b) a high threshold type, extended to all the muscle ("patellar response", for the quadriceps femorae, or response of diffuse localization). *Cohen* has worked on decerebrate cats.

We feel that this brief reference to the present anatomo-functional knowledge relative to the stretch reflex, as well as a proper concept of the relationship of this reflex with the deep muscle reflexes of clinics, a point which we have endeavoured to outline above, will permit a better understanding of the sense and scope of our proposition that in this field the old terms "reflexogenous zone" and "enlargement, increase, or extension of the reflexogenous zone" be substituted by the more correct terms of "zone of provocation" and "enlargement, increase, or extension of the zone of provocation".

Other clinical aspects of the deep muscle reflexes have been dealt with by the author in his previous works.

SUMMARY

The author insists on his proposition (1949, 1950) (7, 8) of substituting, in the case of deep muscle reflexes, the incorrect term of "reflexogenous zone" by the term, much more proper, of *"zone of provocation"*, and consequently he suggests that reference be made to "extension of the zone of provocation" instead of "extension of the reflexogenous zone".

The author reviews the very intimate relationship maintained by the deep muscle reflexes of the clinic with the physiological concept of the stretch reflex. Likewise, he refers to the anatomico-functional concepts of the present time relative to said stretch reflex.

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PETECHIAL CEREBRAL HAEMORRHAGE OWING TO PROFOUND CEREBRAL PHLEBOTHROMBOSIS

Two Cases with Dyspeptic Symptoms

By

SIMON FISCHER

Cerebral phlebothrombosis was first mentioned by *Andrew* in 1865 (1). Thrombosis localized especially to the vena cerebri magna of Galen, the so-called profound phlebothrombosis, was first described by *Parrot* (20) in a child in 1873. However, a more thorough description was given by *Scougal* (22) in 1888. In 1887 *Money* (19) mentioned phlebothrombosis complicated by petechial haemorrhages ascertained at autopsy of a child. Petechiae in cortical venous thrombosis in conjunction with craniotomy have been observed by *Dowman* (10) in 1926, *Davis* (9) in 1933, and *Bernheim* (5) in 1954.

The classification of cerebral phlebothrombosis into primary autochthonous and secondary septic types was mentioned by *Gowers* (13) in 1893 and by *Bristowe* (6) in 1888, respectively.

Of conditions predisposing to primary venous thrombosis, mention may be briefly made of marasmus, anaemia, leukaemia, chronic diarrhoea, birth traumas, haemorrhage in the sinus cavernosus, and intracranial tumours, among which haemangioma may be mentioned in particular. Finally, cerebral phlebothrombosis may occur in heart disease owing to venous congestion. As mentioned by *Kendall* (16) in 1948, there are special conditions to be considered during the puerperium owing to thrombocytosis, increased content of fibrinogen in the blood, shortened clotting time, and possible endothelial lesion during labour.

Secondary thrombosis may be seen in the following diseases: Typhoid fever, tuberculosis, diphtheria, measles, scarlet fever, and such other infectious conditions as otitis media, pneumonia, meningitis, pericarditis, sinusitis paranasalis, dental infections (*Cernea* and *Laufer* (7) 1953) and, finally, in cerebral abscess; this may occur, *inter alia,* after septic abortion by dissemination along venous networks in the vertebral canal.

Up to 1936 the literature contained 26 cases of deep cerebral thrombosis, including *Ehlers* and *Courville*'s (11) 5 cases in 12,500 autopsies. In clinical studies mention is sometimes made of cortical thrombosis verified at craniotomy. In a clinical series of 25 years from the Montreal Neurological Institute, *Stuart et al.* (23) (1951) found a total of 3 cases of verified cortical venous thrombosis. On the other hand, sinus thrombosis is more frequent; *Irish* (15) (1938) thus found 38 cases of thrombosis corresponding to the sinus transversus among 1000 patients with cerebrovascular changes.

Petechial haemorrhagic encephalomalacia apparently only occurs in cerebral venous thrombosis when supplementing factors are contributory. The most important of these are venous congestion and anoxia. Distension of the veins of the central nervous system may be seen in heart disease, or in the presence of local causes with inhibited outflow, e.g. cerebral oedema or increase of the cerebrospinal fluid in the case of haemorrhage into the subarachnoid space, where the meningeal veins are compressed. Finally, venous congestion is observed in the case of tumours with expansive growth.

Like toxic agents, drugs, and infections, anoxia persisting for some time will be responsible for vascular lesions. Mention may be made of a case of carbon monoxide poisoning reported in 1929 by *Cobb* and *Hubbard* (8). On the other hand, arteriosclerosis is of no importance in this connection. It appears from a case dealt with in this department that rupture of the deep veins of the brain after childbirth produced a pure encephalomalacia and no petechiae owing to the outflow to the haematoma.

However, congestion and anoxia are not always of a degree sufficient to develop petechiae in conjunction with phlebothrombosis. The localization is also of importance to the venous occlusion, its extent and the rate at which it spreads. Petechiae will develop especially when the venous occlusion sets on rapidly, is of great extent and localized where the anastomoses are few or undeveloped. In *Bedford*'s (4) experiments on dogs with ligation of the vena cerebri magna of Galen no changes were found, as a ligation does not affect the anastomoses in the same manner as a more extensive thrombosis. *Schlesinger*'s (21) similar experiments on dogs with ligation of the vena cerebri parva of Galen, however, showed some petechiae a few days after the operation owing to the more central application of the ligature. Petechiae in the basal ganglia in the case of deep venous thrombosis are in accordance with investigations of the drainage area of the vena cerebri interna with carmine gelatin. Drainage from the thalamus, the hypothalamus, and the centrum semiovale also takes place directly to this area. Progressive sinus thrombosis may therefore cause changes in the basal ganglia *(Beck* and *Rusell* (2) 1946). Profound cerebral phlebothrombosis complicated by the petechial encephalomalacia localized to the centrum semiovale was mentioned by *Cobb* (8) in 1929, *Hirsch* (14) in 1938, and by *Ehlers* and *Courville* (11) in 1936 in 6 cases in which it was observed that the haemorrhages avoided the cortex and a narrow subcortical zone.

In cortical venous thrombosis, symptoms are seen especially when difficulties in draining involve vital gyri. Thrombosis of the vena cerebri media Sylvii or the vena cerebri centralis Rolandi may thus give rise to pareses or sensitive disturbances, and the symptoms may develop progressively as in Jacksonian epilepsy (*Guillaume* (12) 1943). Severe visual disturbances may be seen in bilateral and extensive cortical venous thrombosis corresponding to the occipital lobes, or in the case of thrombosis of the posterior part of the sinus sagittalis superior. Gastrointestinal symptoms in deep venous thrombosis were mentioned in 7 cases by *Ehlers* and *Courville* (11) in 1936 owing to the changes in the basis cerebri. On the other hand, it is doubtful that primary gastrointestinal disorders with vomiting and diarrhoea leading to dehydration will predispose to thrombosis in the manner often mentioned in the primary type. This must therefore be considered indicative of the importance of the basis cerebri to the function of the intestinal canal.

The diagnosis can be established by angiography (*Lima* (17)) and examination of the spinal fluid with a view to the presence of blood, as haemorrhage often occurs from ependymal ruptures in the thalamic region. At craniotomy, cortical thrombosis and sinus thrombosis can be diagnosed in the area inspected. Depending on the extent of the deep thrombosis, ophthalmoscopy may reveal changes indicative of increased intracerebral pressure with congestion and choking of the discs. In the experiment with ligation of the deep veins, however, ophthalmoscopy showed nothing (*Bedford* (4) 1934).

The prognostic considerations will depend on the extent, the localization and, finally, the underlying cause of the thrombosis. In contrast with the arterial thrombosis, where there is often a small, rather localized massive encephalomalacia, frequently in vital zones, the venous thrombosis causes more extensive, progressive changes of highly varying severity owing to numerous valveless anastomoses.

Treatment is directed against the cause or predisposing factors. Chemotherapy should be used in the case of phlebitis. Further, anticoagulants are of importance in checking progress. For the same purpose, craniotomy and venous excision may be done in cortical thrombosis. But deep venous thrombosis is difficult to deal with surgically. With regard to fluids, cerebral oedema should be mounteracted by avoiding excess administration of liquids, possibly by dehydration also to counteract venous congestion. Anoxia should be avoided by means of oxygen inhalation.

CASE REPORTS

Case 1.—S. 405/55. A man, aged 50. He had been losing weight the last weeks before admission and, during the last few days, had bile-stained vomits with increasing apathy. On admission to Surgical Department A, Københavns Amts Sygehus, Gentofte, the patient was apathetically staring and lean. He had apparently aphasia. His head was turned to the left. The pupils reacted to light, and the optic axes were parallel. The right eye showed no corneal reflex, and the sensibility of the cornea was lowered. There was slight flaccidity of the right half of the face as in slight facial palsy. He had paralysis of the right arm and leg. Slight nuchal rigidity. Left-sided grasp reflex and slight rigidity of the left arm. There was complete absence of reflexes in both arms. Babinski's reflex was bilateral. Hgb. 90 per cent, erythrocyte sedimentation rate 56 mm/1 hr. The patient was highly febrile when death occurred only two days after admission, before lumbar puncture and ophthalmological examination had been performed.

Autopsy findings: An emaciated, prematurely aged man. The cavity of the mouth contained very defective, black, partly broken fragments of teeth. No inflammation or ulcer of the skin of the face and the scalp. The cervical veins, especially the internal jugular vein, were not thrombosed. The respiratory tract contained a purulent secretion originating from the right lung. Lungs: The right lower lobe showed confluent bronchopneumonic processes. The heart was normal. The spleen was marked by infectious hyperplasia. The oesophagus, the stomach and the intestines were normal. The kidneys were pale, somewhat tense. The vena cava inferior with tributaries was not thrombosed. The skull: The theca was thick, eburnated. The middle ears, which were chiselled open, showed no inflammation. Sinus thrombosis was ascertained in the following parts: (1) The sinus rectus (complete). (2) The right sinus transversus. (3) The right sinus sigmoides. (4) The sinus occipitalis (partial). (5) The left sinus transversus (partial). (6) The confluens sinuum with the opening into the vena cerebri magna of Galen. The cerebrospinal fluid was not increased in quantity, not sanguinolent or turbid. The membranes on the base of the brain were injected. The basal arteries were well preserved and free. Sections of the brain showed confluent petechial haemorrhages in: (1) The left caput nuclei caudati and the left thalamus anteriorly, extending a little into the capsula interna and involving 4 sections through the brain in anteroposterior direction. In one section (Fig. 1) a wavy streak of petechiae was seen to pass across the genus of the capsula interna (cortico-spinal and thalamocortical tracts). (2) The right gyrus temporalis superior and medius in 1 to 2

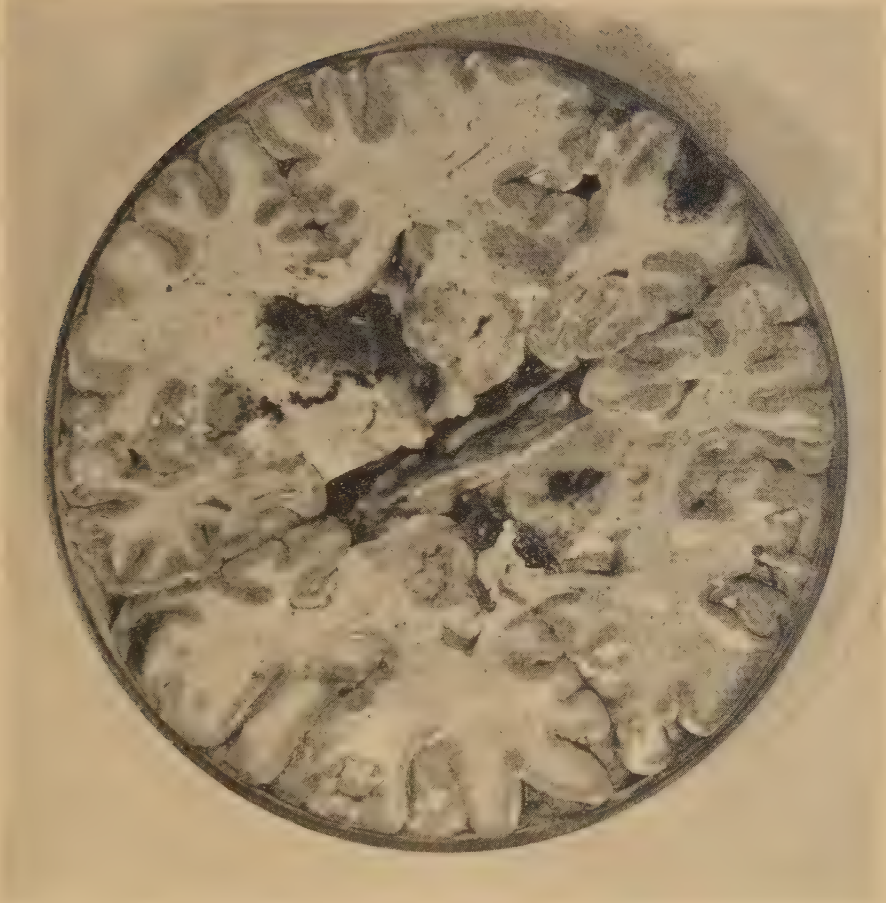

Fig. 1.

sections. A narrow subcortical zone showed some softening there. (3) A few petechiae were seen in the right thalamus. There were no earlier changes.

Histological examination: Sections of the cortex of the right gyrus temporalis showed localized acute inflammation arising from 3 or 4 thrombosed and inflamed veins in the pia. The subarachnoid space contained blood-tinged cerebrospinal fluid with haemosiderophages and vacuolated phagocytes. There were no arterial changes. The phlebitic changes radiated profoundly, and were surrounded by interfascicular fresh haemorrhages in the cortex and the subcortex, arising from dilated capillaries. These haemorrhages appearing in spots extended more profoundly into the centrum semiovale than the inflammation.

Sections from the left thalamus showed acute inflammation arising from about 8 partly subependymal veins with thrombophlebitis and perivenous haemorrhage. Ganglionic cell degeneration was seen in this area. The inflammation progressed along the veins towards the capsula interna and the basal ganglia. The numerous capillary haemorrhages showed a configuration resembling the fascicular nerve pattern.

The plexus choroideus was marked by hyperaemia and oedema, small haemorrhages and phagocytes.

Sections from the anterior part of the velum interpositum showed phlebitis with or without thrombosing of the veins, and a single small abscess-forming focus. In the fornix of this section, similar changes, thrombophlebitis and several petechial haemorrhages were seen.

The vena cerebri magna of Galen was massively thrombosed, but without perivenous inflammation.

The internal jugular vein was normal.

The liver was marked by slight congestion.

The spleen showed infectious hyperplasia.

The kidneys presented no appreciable changes.

Diagnoses: Thrombophlebitis of the cerebral veins.
Petechial haemorrhage owing to capillary congestion.

Case 2.—S. 424/55. A girl, aged 3 months. Delivery had been normal. Already a few days after birth, vomiting occurred after meals, and during the last month before admission she had had liquid motions as well 7 or 8 times daily. The last two days before admission there had been a rise of temperature to about 38° C. On admission to the Paediatric Department, Københavns Amts Sygehus, Gentofte, on June 1st, 1955, the child was slightly dyspnoeic, pale, and with decreased turgor. She appeared rachitic, with rachitic rosary and craniotabes, and was in a state of profound prostration. During the days that followed, she had disgorgements and motions of a gruel-like consistency. The abdomen was distended with gas, and soft. Haemoglobin level from 71 to 89 per cent. There was leukocytosis, rising to 29,400. The phosphatase levels were elevated. The serum calcium level was low, and the serum phosphorus level slightly lowered. Spinal fluid: 710/3 white cells, Pandy's test +++, albumin/globulin: over 50/over 5, spinal-fluid sugar 172 mg per 100 ml (blood sugar: 187 mg per 100 ml). Cultures were sterile. Urine: ++ albumin, + leukocytes. Stools: no pathogenic intestinal bacteria. On June 11th, 1955, a paracentesis was done with evacuation of pus from the right middle ear. The patient was treated with chemotherapy, bicarbonate, blood, and glucose. On June 16th she became unconscious, with a high temperature, somewhat rigid, quivering and restless. The optic axes were parallel and the pupils normal. The consultant neurologist examined the child, and considered the case to be one of secondary encephalitis. The right half of the face was oedematous. Ophthalmological examination: No signs of changes in the vessels or the eye-grounds. She died on June 22nd, 1955, at 3^{30} p.m.

Autopsy showed a female child in a state of medium nutrition, of anaemic appearance and with somewhat mongoloid features. The abdomen was distended. The most essential changes were: The respiratory tract contained a small amount of secretion with an admixture of stomach contents. The lungs were emphysematous. The heart was normally developed. The oesophagus, stomach, and intestine were considerably distended with gas. The stomach had retained some milk dilution. The skull: Slightly increased quantity of fluid, which was blood-tinged. The middle ears were chiselled open, and accumulation of purulent, mucous secretion was seen in the right. The tegmen tympani was intact. The internal jugular veins were normal. Thrombosis was seen in the following veins and sinuses: (1) Both venae cerebri internae et choroideae; (2) the vena cerebri magna of Galen; (3) the sinus rectus with the confluens sinuum; (4) the sinus transversus on either side, though with partial thrombosis in the left; (5) the right sinus sigmoides. Sections of the

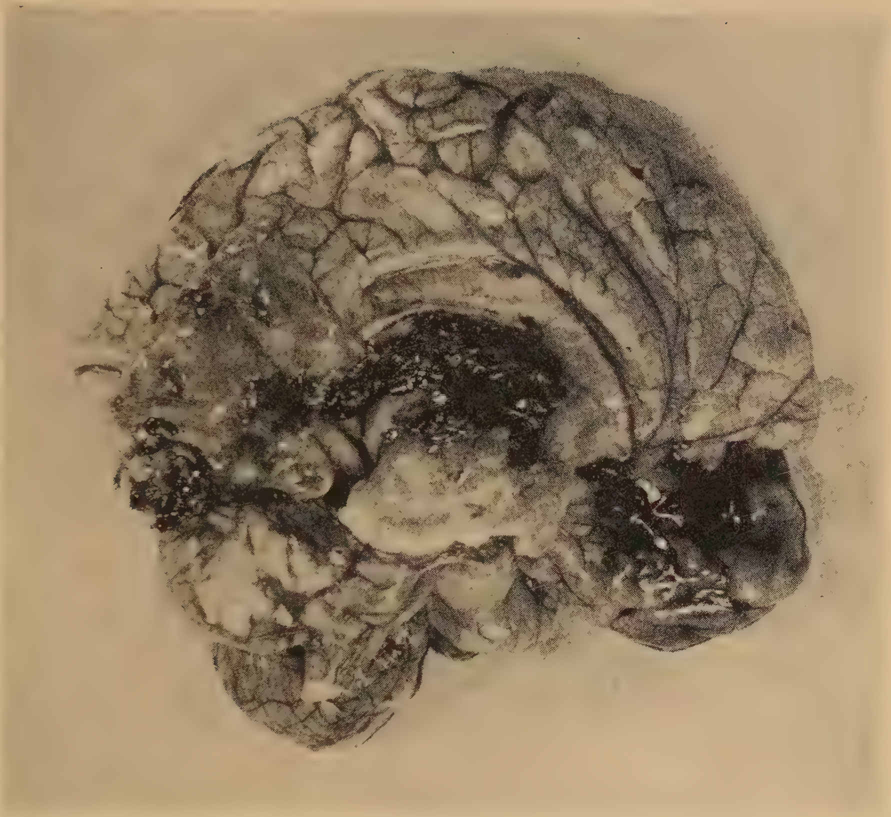

Fig. 2.

brain showed widespread haemorrhagic infarction, localized to the thalamus, the basal ganglia, the capsula interna and the centrum semiovale; sagittal sections of this showed strands of stippled or petechial haemorrhages and some softening of the tissue. The changes did not involve either the cortex or the subcortical tissue. The plexus choroideus was of a deep red colour, showing haemorrhage from the lateral ventricles. The posterior part of the fornix showed stippled sagittal haemorrhages (Fig. 2). Histological examination of the sinus rectus with the vena cerebri magna of Galen: Massive thrombosis but no perivenous inflammation. The thalamus: Beneath the ependymal lining several thrombosed small veins were seen. The thromboid clots were to some degree infiltrated with polymorphonulear leukocytes. No definite organization of the thrombosed veins was seen, and there was only very slight perivenous leukocyte reaction. The nerve tissue present was marked by haemorrhagic infarction owing to confluent petechial haemorrhages seen in relation to the dilated capillaries. No meningeal inflammatory changes. The cortex showed no signs of anoxia. Gram-staining revealed no bacteria. The plexus choroideus: Several small veins were thrombosed, but there was little or no leukocytic reaction.

Diagnoses: Thrombosis of the cerebral veins.
Petechial haemorrhage owing to capillary congestion.

SUMMARY

After a complete survey of cerebral venous thrombosis, reports are given of two cases of deep thrombosis, one in a man, aged 50, the other in a girl, aged 3 months. Both had dyspeptic symptoms. The thrombosis apparently originated from very defective teeth and from suppurative otitis media, respectively. Autopsy showed centrally confluent petechiae in the brain in relation to the dilated capillaries, whereas the cortex seemed chiefly uninvolved. Venous blocking should thus be borne in mind as a fundamental cause of petechiae.

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EPILEPSY FOLLOWING RADICAL REMOVAL OF PARASAGITTAL AND CONVEXITY MENINGIOMAS

By

GÖSTA FLYGER

It has long been known that epilepsy may appear after injuries to the head. These injuries may either be the result of an accident to the head or caused by operative intervention in the brain. Patients with brain-tumours, who before operation have not had any attack of epilepsy, may therefore after an otherwise successful and radical operation develop convulsive seizures. This is the more unfortunate as these seizures may be the only symptom after operation.

The brain-injury may lead to epilepsy of different type and severity, but some parts of the brain are more epileptogenic than others. Irrespective of their pathological substratum injuries situated in or near the central sulcus show the greatest frequency of producing epilepsy (*Penfield & Erickson* (9), *Walker* (10)). As to other parts of the brain there is no unity. Some authors declare that frontal injuries show the greatest frequency of producing epilepsy, others are of the opinion that there is a predominance for occipital and temporal injuries (*Ascroft* (1), *Gliddon* (5), *Credner* (2)). Petit mal and psychomotor attacks seem to be provoked by injuries in the diencephalon (*Jasper* (6)).

A large number of articles dealing with the frequency of epilepsy have been published, but there are very few reports on epilepsy only appearing after operation for brain-tumour. Nevertheless it must be considered important to be able to make a prognosis in this respect, above all when a tumour has been radically removed and the patient is to be considered as cured.

Penfield & Erickson (9) have given an account of 21 patients suffering from meningeal fibroblastomas who were all radically operated on and who before operation had had no symptom of epilepsy. Out of these 9 (42.8 per cent) later developed epileptic attacks. These generally started within 6 months. *Cushing & Eisenhardt* (4) report 51 cases of parasagittal meningiomas, 17 of whom had had no epileptic fits before operation. Among these 17 there were 6 (35.2 per cent) who later developed epileptic seizures. The follow-up time was up to 25 years. The same authors have also given an account of their experience as to 44 cases of radically operated convexity meningiomas. However, only 13 can be considered in this connexion, almost half of whom later developed epilepsy.

The purpose of this work is to examine the postoperative frequency of epilepsy in patients who have been radically operated on because of parasagittal or convexity meningiomas, and who before operation had no epilepsy. Other questions in this connexion are the postoperative frequency of epilepsy in relation to different parts of the brain, the severity of epilepsy, and the problem how it can be controlled with antiepileptics.

MATERIAL

Up to 1948 219 patients suffering from parasagittal meningiomas (p. s. m.) and 94 patients with convexity meningiomas have been treated at the Serafimer Hospital. Contrary to *Cushing* (3) we have among the p. s. m. also included meningiomas arising from the falx. However, only patients without anamnestic epilepsy are included; hence the material worked up consists of 47 cases of p. s. m. and 31 cases of convexity meningiomas.

The distribution of the two tumour-groups appears from Tables 1 and 2. The location of the p. s. m. is based on the situation of their attachment to the dura, *Olivecrona* (7, 8). In both tumour-groups there are cases in which the tumour was situated on the border between two regions. There were 9 such cases in the p. s. m.-group, 8 situated on the border between the anterior and middle third of the sinus and 1 between the middle and posterior third. In these cases the tumour was considered to be localized to the part where it had its largest mass.

The convexity meningiomas have been classified into frontal, parietal, occipital, and temporal. The limits of these regions are the ordinary anatomical ones, yet with the exception that the posterior limit of the frontal lobe has been placed in the precentral sulcus. The p. s. m. are often bilateral, thus in 7 of the present cases.

The operative technique used in connexion with the p. s. m. has followed the rules described by *Olivecrona* in his monograph of 1934 and we have been very restrictive as to resection of the sinus. Only if the sinus has been wholly occluded by tumour-tissue we have carried out a bloc-resection. In other cases we have contented ourselves with a

TABLE 1

Location of p. s. m. and postoperative frequency of epilepsy.

	Total	Convuls.	No convuls.
Anterior third	22	12	10
Middle third	12	11	1
Posterior third	13	0	13

TABLE 2

Location of convexity meningiomas and postoperative frequency of epilepsy.

	Total	Convuls.	No convuls.
Frontal	24	7	17
Parietal	4	2	2
Temporal	1	0	1
Occipital	2	0	2

marginal resection, and in a few cases there has been practically no resection at all. Our endeavour has always been to make the resection as small as possible. There are no recurrences in this material nor cases with postoperative wound infection. None of the patients has had any hereditary tendency to epilepsy.

The follow-up time ranges between 3 and 20 years and the results are based on the correspondence conducted by the clinic with all patients discharged.

RESULTS

The postoperative frequency of epilepsy is recorded in Tables 1 and 2. It is remarkable that no patient suffering from a p. s. m. in the posterior third of the sinus has had any attack of epilepsy postoperatively. On the other hand, when the meningiomas have been situated in the middle third, epileptic seizures have appeared in almost every case and also meningiomas from the anterior third have a rather great epileptic frequency, about half of the cases.

The convexity meningiomas give other figures. Tumours situated in the frontal lobe have led to epileptic fits in about one third of the cases only. As to other parts of the brain the figures are too small to permit a distinct statement, but for the occipital convexity meningiomas there is good consistency with the p. s. m.

The 9 patients with convexity meningiomas who after operation have developed epileptic seizures, have all got it during the first two years, most of them already during the first year. As to the p. s. m. the facts are about the same with a collection of the starts of epileptic fits during the first two years. In 5 cases out of 22, however, the epileptic seizures have appeared later, in one case not before five years after operation. This wider range for the p. s. m. may partly be explained by the fact that this material is greater. See Tables 3 and 4.

TABLE 3

The appearance of postoperative epilepsy among the p. s. m.

	Years						
	1	1—2	2—3	3—4	4—5	5—6	6—7
Anterior third	5	4	1			1	
Middle third	6	3	2	1			
Posterior third							

TABLE 4

The appearance of postoperative epilepsy among convexity meningiomas.

	Years				
	1	1—2	2—3	3—4	4—5
Frontal	4	3			
Parietal	2				
Temporal					
Occipital					

TABLE 5

Postoperative type of epilepsy.

Type of tumour.	Location	Jacksonian	Grand mal
P. s. m.	Anterior third	6	5
	Middle third	12	
	Posterior third		
Convexity meningiomas	Frontal	0	7
	Parietal	1	1
	Temporal		
	Occipital		

Postoperative epilepsy partly consists of grand-mal attacks with unconsciousness and general convulsions, partly of Jacksonian fits with or without unconsciousness. In a few cases there have been a combination of both, but there has always been predominance of one form. No other forms of epilepsy have been recorded. The distribution and type of epilepsy appears by Table 5.

DISCUSSION

Out of 313 patients suffering from p. s. m. or convexity meningiomas 71 (24.9 per cent) had no preoperative epilepsy. Compared to investigations by *Penfield* and *Erickson* (9) these figures are rather low. Among 63 meningiomas situated above the tentorium, the above-mentioned authors found that 33 per cent had no anamnestic epilepsy. In part the difference can be explained by the fact that the latter series also contains meningiomas situated in other locations than parasagittally and on the convexity. In the series under consideration (78 cases) postoperative epilepsy appeared in 41.1 per cent (32 cases). Here the accordance with the results obtained by *Penfield* and *Erickson* (9) is better. Among 29 patients without preoperative epilepsy they found it postoperatively in 42.1 per cent.

The p. s. m. have a considerably higher frequency of epilepsy postoperatively (48.9 per cent) than have the convexity meningiomas (29.3 per cent). The difference is too great to be explained only by the fact that the two groups differ appreciably in size. Several other facts should be emphasized. Relatively more p. s. m. were situated in or near the motor centres, and merely from that fact it is justifiable to expect a higher frequency of epilepsy. It should also be taken into consideration that most of the p. s. m. frequently are bilateral or at least have invaded the sinus. The surgical removal, therefore, must be technically more difficult, with rather more trauma to the brain and thus the risk of postoperative epilepsy must be greater. The great difference is therefore nothing to be wondered at.

Concerning the distribution of postoperative epilepsy to different regions of the brain, it is evident from Tables 1 and 2 that parietal tumours show the highest frequency, and nothing else was to be expected. It is also obvious that the occipital lobe is epileptogenic to a considerably less degree than the frontal lobe. It is true that the occipital tumours in this series were not wholly restricted to the occipital lobes, but partly situated within the parietal lobes. But at least one of the reasons for the lower frequency of postoperative epilepsy may be that the occipital tumours are situated farther away from the motor centres.

Practically no patient has been given any antiepileptic treatment until the epileptic seizures appeared. Formerly they got Phenemal in optimal doses but during the latest years we have combined Difhydan (Phenantoin), Antilepsin (diferrylhydantoin), or Tridion (3,5,5,-trimetyloxazolidin – 2,4 – dion) with Phenemal. Only 5 patients out of 32 have been unimproved with such treatment. All 5 cases were patients with tumours in or near the central sulcus; 4 had p. s. m. and 1 convexity meningiomas. Of the remaining patients 11 have been free from attacks for a number of years (3–20 years), so there is reason to presume that the effect will be permanent. 16 patients have improved but are not entirely free from attacks. Yet the attacks are not so severe as to prevent them from working. Then, it seems advisable to start the antiepileptic treatment as soon as possible, because in this way we have a further opportunity of reducing the postoperative frequency of epilepsy.

SUMMARY

Postoperative epilepsy in patients operated on because of parasagittal meningiomas or convexity meningiomas and who have had no anamnestic epilepsy nor any hereditary tendencies to epilepsy appears in 41.1 per cent. The p. s. m. show a considerably higher frequency of epilepsy postoperatively than the convexity meningiomas, 48.9 and 29.3 per cent, respectively.

Although antiepileptic treatment has not been instituted until epileptic seizures appeared, the results obtained have been rather fair. If the treatment is instituted as soon as possible the results will certainly be still better.

This paper is one of a series presented to Professor H. Olivecrona on his 60th birthday.

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PRIMARY SENSORY NEUROPATHY IN A CASE OF BRONCHOGENIC CARCINOMA

By

N. A. Lassen and O. Munck

In 1948 *Denny-Brown* published two cases of primary sensory neuropathy associated with bronchogenic carcinoma. The neurological symptoms consisting of universal paresthesia, hyp- or anaesthesia of hands and feet, impaired deep sensitivity, ataxia, and hypotonia preceeded the pulmonary symptoms for several months. Post-mortem examination revealed anaplastic bronchogenic carcinoma without relevant secondary deposits, degenerative lesions of the spinal ganglia, of the posterior columns of the spinal cord, of the posterior roots of the spinal nerves, and partially of the peripheral nerves. Furthermore he described degenerative muscular changes—but apart from general weakness no muscular symptoms had been present. *Denny-Brown* emphasised that the symptoms of pronounced symmetric deafferentitation with only indistinct motor disturbance were remarkable. Since *Denny-Brown* reported these two cases only five more cases of the syndrome with a complete post-mortem examination have been published (*Wyburn-Mason* (1948), Case 1; *Henson, Russell,* and *Wilkinson* (1954), Cases 7 and 8; *Healthfield* and *Williams* (1954), Cases 1 and 2).

CASE REPORT

A working man, aged 55, was admitted to the Kommunehospital, Copenhagen, on August 28th, 1954 (Dep. III No. 1561/54). Seven months previously he had developed pricking pains in the back of his head and in the right shoulder region accompanied by some weakness of the right arm, and pins and needles in the right hand. During the following months the sensory symptoms spread to the left arm, and his walking grew unsteady. At that time he was unable to work. He consulted a neurological specialist (*K. H. Krabbe,* M.D.), whose findings were consistent with those obtained at the admission one month later. A diagnosis of polyneuritis was made, and a treatment with vitamin B_1 was given. However, the sensory symptoms aggravated, as—especially in hands and feet—a universal sensation of pins and needles on touch developed. He suffered from general weakness, but not from elective paresis. In August 1954 he was so disabled and suffering from the neurological symptoms described that hospitalization was necessary. It should be mentioned that he had not been exposed to lead nor to any noxious fumes. He had occasionally drunk beer, never spirits. Pulmonary symptoms of three months' duration were disclosed only by direct inquiry on admission; he had been suffering from mucopurulent expectoration and dyspnoea on exertion. For 40 years he had been smoking about 20 cigarettes a day.

Examination disclosed a moderately wasted man with a pale greyish colour and impaired breathing. There were signs of consolidation in the upper part of his left lung. In the left supraclavicular region several enlarged lymph nodes were found. Nothing abnormal was palpable in the abdomen. Cranial nerves: apart from moderate paraesthesia in the face and hypaesthesia of the corneae nothing abnormal was found. The limbs were hypotonic and flabby with some generalized weakness, most pronounced in the left arm. Sensation to light touch was abnormal all over, as paraesthesia was produced, especially by touching the fingertips. No anaesthetic regions were found. Pain and temperature sensation were unimpaired. The position sense was slightly impaired. Diadochokinesis was somewhat reduced, and the coordination tests revealed gross ataxia of all extremities. There was marked Rombergism, and the gait was unstabe. The tendon reflexes were uniformly weak in the upper limbs and absent in the lower limbs. The plantar reflexes were flexor on both sides. Other investigations revealed: normal hemoglobin contents, no gastric achylia, elevated ESR, and normal urine analyses. The CSF was clear and colourless with 3 cells per c.mm., the total protein 12 mg per 100 ml, and the Wassermann test negative. Blood WR and Kahn were also negative. The blood pressure and acid phosphatases of serum were normal. X-ray of the chest showed in the left lung a dense shadow irradiating upwards from the hilus. Histological examination of biopsy from lymph nodes in the left supraclavicular region confirmed the clinical diagnosis of carcinoma of the bronchus. The patient succumbed to terminal pneumonia on September 8th, 1954, seven months after the onset of the peripheral neuritis and three months after the onset of pulmonary symptoms.

ANATOMICAL FINDINGS

The left lung contained a large tumor in the upper lobe and pneumonic consolidations in the lower lobe. The right lung was normal. Secondary deposits were found in the left pleura and in the lymph nodes of the left hilus, the mediastinum, and the left supraclavicular region. The brachial plexus was not invaded. Slight atheromatosis of the aorta and the coronary arteries was present. The kidneys contained some congenital cysts, but were otherwise normal. Heart, liver, spleen, stomach, intestine, suprarenals, bladder, and prostate were healthy.

10 per cent. neutral formalin was injected in the subarachnoidal space immediately post mortem. The central nervous system appeared normal on external examination. The brain was cut in coronal sections and revealed nothing abnormal, whereas in the spinal cord numerous horizontal sections disclosed a whitish discoloration of the posterior columns.

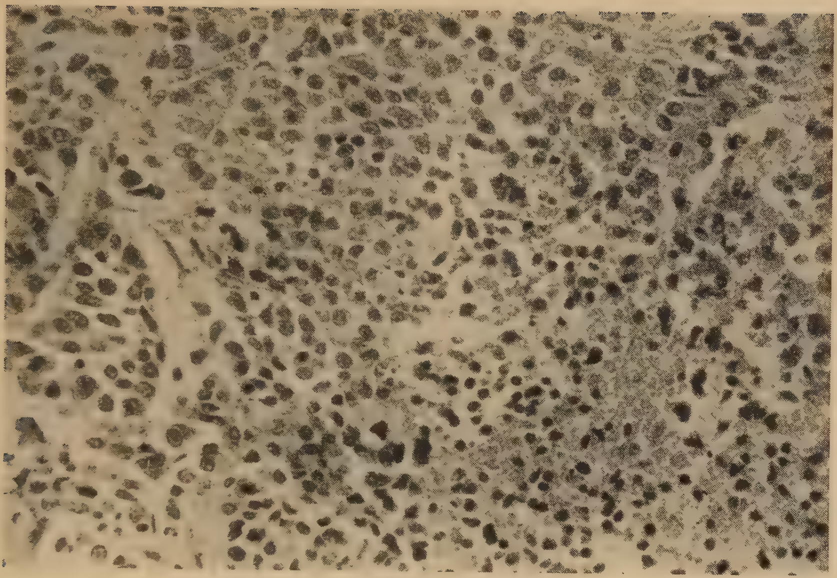

Fig. 1.
Lung tumor. Hematoxylin and eosin. × 280.

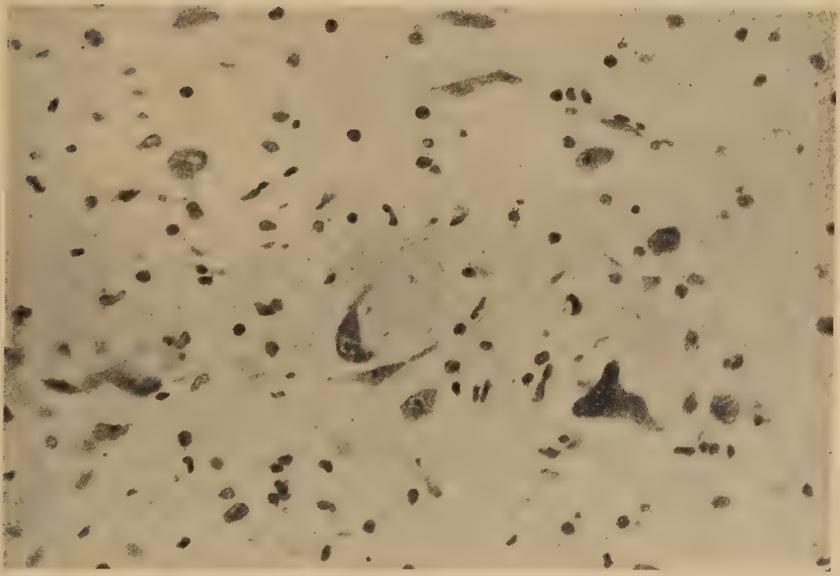

Fig. 2.
Cuneate nucleus showing degeneration of nerve cells and gliosis. Gallocyanin. × 280.

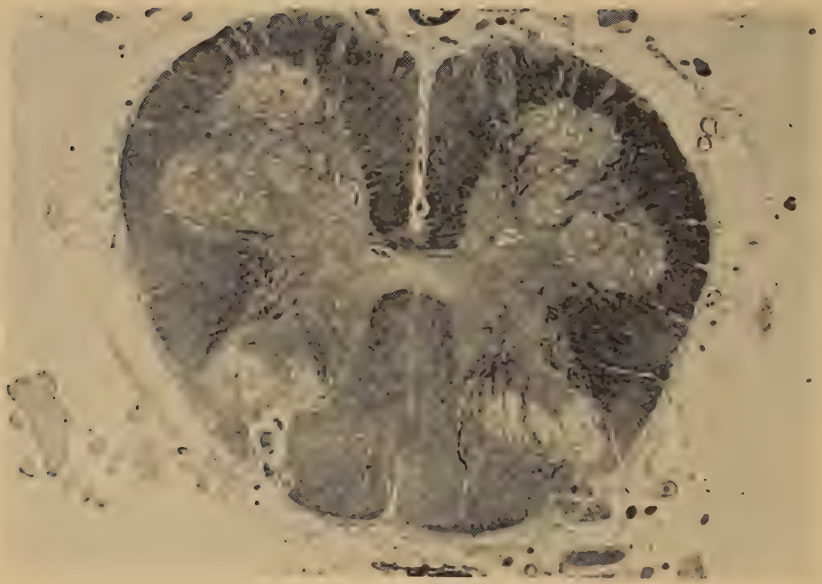

Fig. 3.
Third lumbar segment showing degeneration of posterior columns. Weil. × 11.

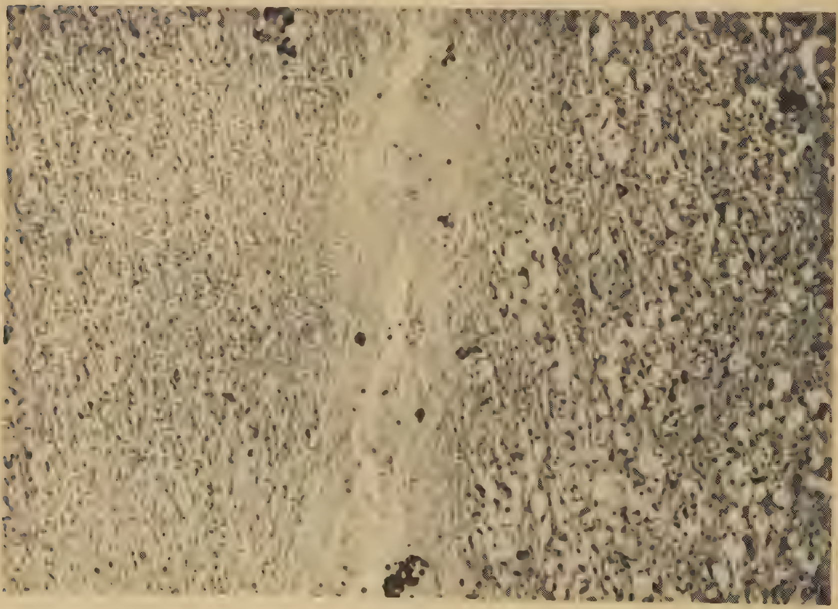

Fig. 4.
Lateral (left) and posterior (right) columns of third lumbar segment to show degenerative lesions of the posterior column. Weil. × 145.

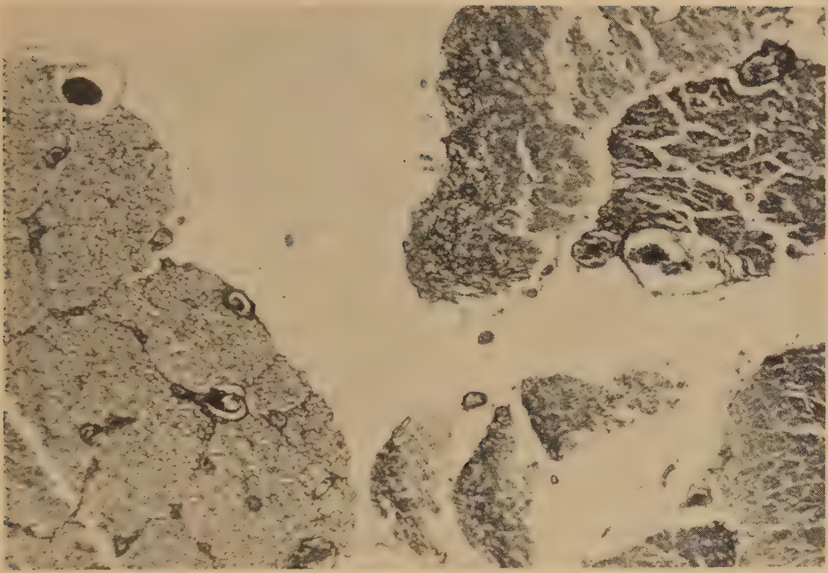

Fig. 5.
Cauda equina showing degeneration of posterior root and normal anterior root.
Mallory (Russell's modification). × 145.

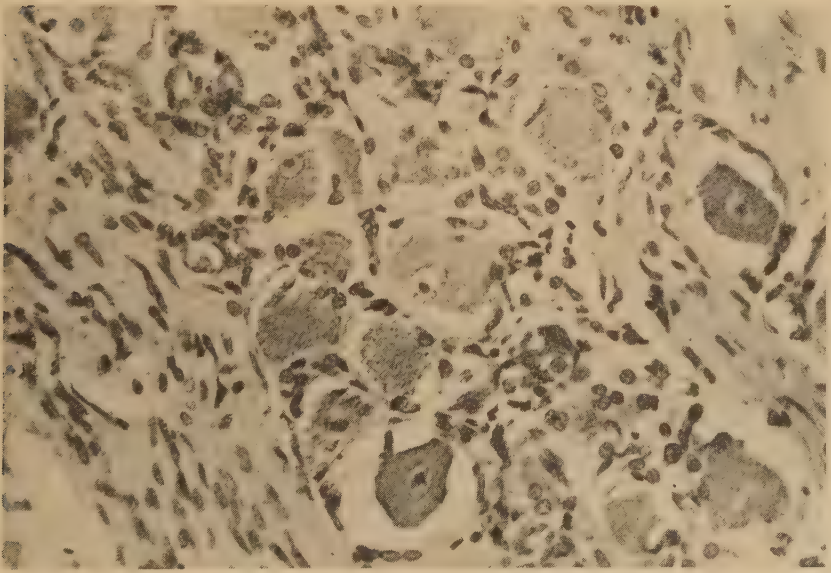

Fig. 6.
Right sixth cervical dorsal root ganglion showing various degrees of degeneration and loss of dorsal root cells together with proliferation of the oligodendroglial cells, especially on the place for the completely degenerated nerve cells.
Hematoxylin and eosin. × 280.

Histological Examination (Performed by Erna Christensen, M.D.).

Sections of the lung, supraclavicular lymph nodes, pituitary gland, of various levels of the spinal cord, brain stem, cerebellum, and cerebrum, of the right sixth cervical dorsal root ganglion, of the anterior and posterior spinal nerve roots at various levels, including the cauda equina, the left posterior tibial nerve, and of the left soleus muscle were taken and stained by a variety of methods. The tumor of the lung consisted of small polygonal epithelial cells with large darkly stained nuclei (fig. 1). Some mitotic figures were seen. The cells were arranged in solid formations and invaded the surrounding tissue. Similar growths were present in the regional lymph nodes. A diagnosis of anaplastic carcinoma of the bronchus was made. The pituitary gland, the brain stem, the cerebellum, and the cerebrum revealed nothing abnormal. Degeneration of nerve cells, demyelisation of nerve fibres, and marked gliosis were found in the gracile and cuneate nuclei (fig. 2). Profound and diffuse but not complete degeneration was found throughout the posterior columns of the spinal cord without any inflammatory reaction (figs. 3 and 4). The posterior nerve roots were severely degenerated, as only occasional myelinated fibres were seen (fig. 5). The anterior nerve roots were normal. The posterior root ganglion examined was profoundly altered, as various degrees of degeneration and loss of dorsal root cells were present together with proliferation of the oligodendroglial cells especially in the place of the completely degenerated nerve cells (fig. 6). The peripheral nerve showed a mixture of intact and degenerated nerve fibres, whereas nothing abnormal was found in the muscle examined.

DISCUSSION

A coincidence of neuropathy and tumor cannot be precluded from one case. But by comparing our case with the seven well examined ones previously reported, a striking conformity in regard to symptomatology as well as in pathological findings is apparent, as all the patients suffered from a peripheral sensory neuropathy beginning several months before the onset of pulmonary symptoms, and the histological findings uniformly revealed degenerative lesions of the dorsal root ganglion cells with presumably secondary degeneration in the central nervous system and in the peripheral nerves. Moderate atrophy of the cross-striated musculature has been described in some of the cases.

To our knowledge this neurological disorder has only been described in association with bronchogenic carcinoma. However, *Dodgson* and *Hoffman* (1953) described a case of mixed motor and sensory neuropathy associated with an undifferentiated carcinoma of the oesophagus, where the sensory symptoms as well as the related—but incomplete—pathological findings closely resembled the neuropathy in question. It is noticeable that the histological picture in all cases has been that of an anaplastic carcinoma. No explanation of the nature of the syndrome can be offered on the cases so far reported, but it has been suggested by *Denny-Brown* (1948) that even sub-clinical malignant growths might influence the metabolism of the nerve cells in the spinal ganglia.

Apart from metastatic deposits, and differing from the described sensory neuropathy, the following degenerative disorders occur associated with carcinomatous diseases:

(1) subacute cerebellar degeneration associated with carcinoma of lung, breast, ovary, and uterus (*Brain, Daniel,* and *Greenfield* (1951); *Henson, Russell,* and *Wilkinson* (1954)).

(2) mixed motor and sensory polyneuritis associated with carcinoma of the bronchus (*Lennox* and *Prichard* (1950); *Elkington* (1952); *Henson, Russell,* and *Wilkinson* (1954); *Heathfield* and *Williams* (1954)).

(3) myopathy resembling myasthenia gravis associated with carcinoma of the bronchus (*Henson, Russell,* and *Wilkinson* (1954); *Heathfield* and *Williams* (1954)).

An excellent review on neurological disorders in carcinomatous diseases has recently been published by *Henson, Russell,* and *Wilkinson* (1954), who described 19 cases, among which all the syndromes referred to were found. Carcinoma of the bronchus was present in 17 cases. In no less that 10 cases of that series the bronchial carcinoma was found as a result of a search suggested by the neurological findings. Such a diagnosis has never resulted in a successful removal of a bronchogenic carcinoma.

Among the neurological disorders described in association with malignant diseases it appears that the syndrome of *Denny-Brown* is the most conspicuous and the one best examined. This opinion was also expressed by *Heathfield* and *Williams* (1954) who concluded: "The primary sensory neuropathy is in our opinion so characteristic of the syndrome that even if the chest X-ray shows nothing abnormal, bronchoscopy should be invariably performed."

SUMMARY AND CONCLUSION

(1) A case of primary sensory neuropathy associated with anaplastic carcinoma of the bronchus is described.

(2) The clinical and pathological findings are in agreement with those reported in the literature.

(3) The recognition of the neurological symptoms may lead to the discovery of lung tumors otherwise silent.

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GUILLAIN-BARRÉ SYNDROME WITH PROMINENT SPINAL AND CEREBRAL PHENOMENA

Treated with ACTH (Corticotropin)

Complicated with Retroperitoneal Bleedings

By

ARVE LØNNUM

Since *Guillain*, *Barré* and *Strohl*'s important publication of 1916 many works have been published upon this syndrome, with a tendency to extend the syndrome to comprise even cases with encephalitic and myelitic symptoms and signs.

Guillain and *Barré* themselves opposed this tendency in a number of works. But *Guillain* has lately reported several cases with *spinal* as well as *cerebral* manifestations (1953).

In most reports, however, the disturbances of cerebral and spinal function have been less severe than the striking ones observed in the following case. In spite of these disturbances the patient will clearly disclose a clinical picture which in most respects suggests a Guillain-Barré syndrome.

CASE REPORT

L. K. 63 year old man. R. H. L. no. 16426/54 and 12890/55.

Admitted to the Department of Neurology, Oslo University Hospital (Rikshospitalet) from June 27, 1954, to August 2, 1954. Readmitted from March 24, 1955, to April 30, 1955.

The patient had never been seriously ill before. From June 4, 1954, he suffered from an upper respiratory tract infection lasting for a few days and accompanied by a stiffness in his neck. Nine days later he noticed irradiating pain in the posterior part of both legs. After four days more he felt in both legs, especially in the right one, a weakness which very soon also spread to both arms. On admission to a county hospital June 18, 1954, the spinal fluid was found normal. During the following days an ascending paresis increasing to paralysis appeared, with complete absence of deep and cutaneous reflexes. On June 25 a bilateral facial paresis of peripheral type was noticed simultaneously with impaired respiration. On the same day examination of the spinal fluid revealed one cell in each ml. of fluid, while the Pandy test was decidedly positive.

On June 27 the patient was transferred to the Department of Neurology, Oslo University Hospital. Before his discharge from the county hospital and during the long transport the condition of the patient was constantly growing worse, and increasing aphasia and somnolence indicated severe cerebral involvement.

On admission the body temperature was normal. The sedimentation rate was slightly elevated (27 mm. per hour). The differential count in the peripheral blood was normal. The pulse rate was 100, regular, and the blood pressure was 150/100. But the pulse rate and the blood pressure showed marked fluctuations during the first week. The pulse rate varied from 60 to 130, and the blood pressure varied from 110 to 170 systolic, and from 80 to 100 diastolic. Electrocardiographic examination only showed signs of sinus tachycardia.

On admission the routine examination demonstrated no signs of disease in organs other than the nervous system. The clinical findings suggested polyradiculoneuritis with an addition of spinal and cerebral symptoms. Among the latter the most outstanding were widespread fasciculations and a peculiar mental state. He would in no way cooperate during the examination. This behaviour was attributable neither to the motor nor the sensory deficiency, nor to somnolence, for at times he clearly showed that he was awake by the fact that the would pay attention to the door being opened and to the attendants passing to and fro. On firm supraorbital pressure he would pull a face, but otherwise it was difficult to obtain a reaction to any external stimulus. The spinal fluid contained no cells, whereas the Bisgaard test was positive in a dilution 1 to 40, indicating a distinct increase in protein. EEG showed very marked generalized cerebral dysrhythmia (fig. 1).

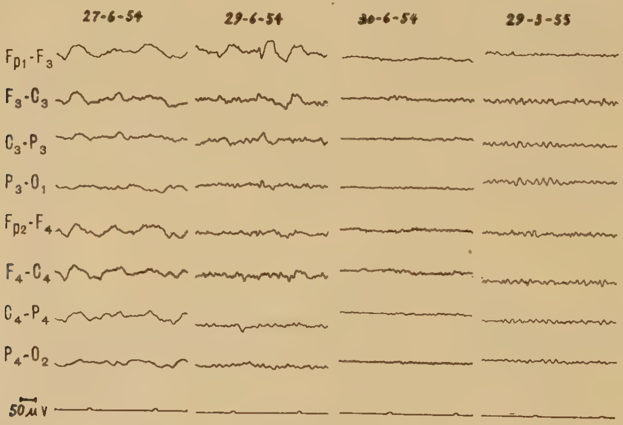

Fig. 1.

EEG at different stages in a case of the Guillain-Barré syndrome. First tracing on admission to the Neurological Department, Oslo University Hospital, on June 27, 1954. EEG shows marked generalized cerebral dysrhythmia. Clinical symptoms severe. Tracings 2–3 on the 2nd and 3rd day after admission show rapid changes towards normalization. Tracing 3 shows only signs of a focal lesion, possibly epileptogenic, in the left frontal region. Clinical improvement. Tracing 4, about 10 months later, shows a normal EEG. No symptoms left besides nervousness.

The quick and steady progress of the disease seemed to predict a very bad outlook for the patient if an effective treatment could not be found. Because of many favourable reports of ACTH-(corticotropin)-treatment in cases with the Guillain-Barré syndrome (see below), corticotropin was immediately given. Post or propter a marked change in the patient's condition was observed. Respiratory troubles disappeared, and two days later he cooperated so well during the examination that it was possible to prove a loss of superficial sensibility with a radicular distribution distally in the right leg. In the same area increased sensitivity to deep pressure and reduced sense of position were noted. Despite a motor as well as a sensory aphasia, the patient could speak a little. There was, however, a good deal of perseveration. At this time, and even more later on, one was struck by the patient's non-spontaneous behaviour.

In two days the EEG showed striking changes towards normalization, this being even more obvious on the third day, although signs of a more focal lesion in the left frontal region, possibly epileptogenic, were still present (fig. 1). A marked reduction of the protein in the spinal fluid was evident from the Bisgaard test, which was positive in a dilution of 1 to 15, only slightly above normal values. (See legend to fig. 2, which shows the normomastic curves at different stages of his illness).

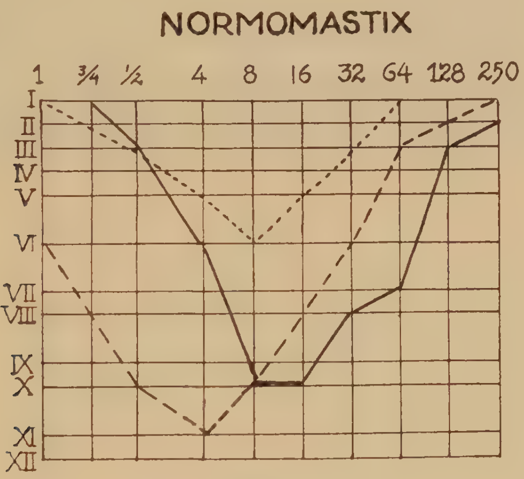

Fig. 2.

Normomastix curve in a case of the Guillain-Barré syndrome. A spinal fluid examination on June 18, 1954, showed no increase in cells or protein, whereas the Pandy test on June 25 was decidedly positive. First curve (indicated by - - - -) on admission to the Department of Neurology on June 27. The Bisgaard test was positive in a dilution 1 to 40. Three days later this test was positive only in a dilution 1 to 15. Second curve on July 25 (indicated by ———). Bisgaard test slightly positive in a dilution 1 to 10. Third curve on March 23, 1955 (indicated by – – – –). Bisgaard test only showed traces of protein in a dilution 1 to 10.

After a striking improvement, which continued for some days, the symptoms and signs of neurological illness receded more slowly for weeks and months, as shown in fig. 5. This slower recovery continued even when on the 11th day after admission corticotropin treatment was stopped, on account of acute abdominal illness, the

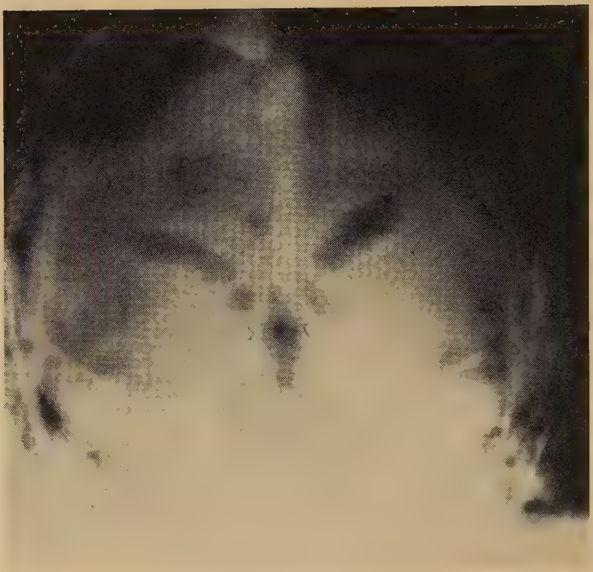

Fig. 3.

Figs. 3–4: Pneumoencephalography April 18, 1955, in a case of the Guillain-Barré syndrome, about 10 months after start of the illness. Slight dilatation of 3rd ventricle (fig. 3) and of left lateral ventricle (fig. 4), indicating some permanent damage to the brain.

nature of which at this time was quite obscure. But in 24 hours the hemoglobin value was reduced from 95 to 58 per cent, and 48 hours later a diffuse mass could be palpated in the abdomen above the umbilicus. In spite of extensive investigations, including X-rays of the gastro-intestinal tract, no source of the bleedings could be found. Blood examinations revealed no hemolytic tendency or other pathological conditions, which could explain the acute anemia. There occurred no hematemesis or melæna, neither was there any free fluid in the intraperitoneal cavity. The anemia therefore was looked upon as being caused by retroperitoneal bleedings of unknown origin.

In one month two similar bleedings occurred at a time when no specific treatment was given. After blood transfusions the patient each time recovered from the bleedings, which seemed in no way to influence the course of the neurological disease.

Despite the hemorrhages the patient had improved so much that on August 2, 1954, he could be transferred to a county hospital for further care. The aphasia, which was accompanied by dyslexia, dysgraphia, and dyspraxia, had vanished gradually in the course of six weeks. The fasciculations in his face, arms, and trunk disappeared after three weeks. Most annoying to the patient at his discharge was an intractable insomnia. The non-spontaneity, so impressive on admission, was still present. The patient would usually do nothing at all, not even drink or eat without being directly called upon to do so. A fortnight before his discharge the reflexes began to return. For some days there was an extensor response of the plantar reflex on the right side, then shifting to a flexor response.

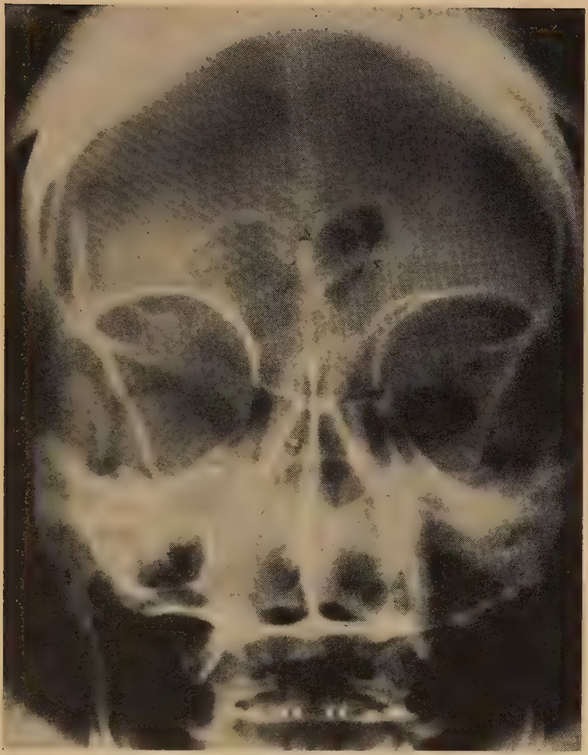

Fig. 4.
Text: Fig. 3.

Otherwise the polyradiculoneuritic symptoms and signs now dominated the clinical picture, in marked contrast to that on admission. But some time after his discharge from the Neurological Department the patient had three epileptic seizures with initial loss of consciousness and generalized convulsions. One seizure was characterized by automatic behaviour. Antiepileptic drugs were given, and no more seizures have been observed.

On March 23, 1955, the patient was readmitted to the Department of Neurology, Oslo University Hospital, for control examination. He reported that since his discharge he had been steadily recovering. The weakness in his legs and the radicular pains were the latest symptoms to disappear. He felt quite well, but complained of some nervousness.

On neurological examination no pathological findings were encountered apart from absent Achilles reflexes in both legs. The other reflexes, however, were now normal. Pneumoencephalography revealed slight cerebral atrophy (figs. 3–4), a finding compatible with the results of psychological tests, including Rorschach, which indicated cerebral dysfunction of an organic character. EEG on the contrary was now entirely normal (fig. 1), and so was the Bisgaard test in the spinal fluid. Even the normomastix curve, in contrast to the earlier observations, showed only minor aberrations.

DISCUSSION

Polyradiculoneuritic symptoms and signs associated with albumino-cytological dissociation in the spinal fluid would suggest that this is a case of the Guillain-Barré syndrome, despite the marked evidence of central nervous system involvement.

There are many conditions in which a Guillain-Barré syndrome is known to occur. Among them are: *Mononucleosis infectiosa* (*Landes* & others 1941, *Vaughan* & others 1946, *Parker & Adams* 1947, *Klövstad* 1950, *Klövstad & Vinje* 1950, *Klein* 1954, *Reske-Nielsen & Mortensen* 1955). *Leucemia* (*Oulie* 1953). *Porphyria* (*Brock & Davison* 1947). *Hepatitis* (*Parker & Adams* 1947). *Hypersensitivity to PAS* (*Bulley* 1954). *Anthrax* (*Goebel* 1898). *Gastro-enteritis* (*Chusid & Marquardt* 1945).*Virus pneumonia* (*Stanton* & others 1953). *Diphtheria, diabetes, serum-inoculations* and *lupus erythematosus* (*Woltman & Kernohan* 1955).

As our investigations could prove none of these conditions to be present in this patient, the most possible diagnosis seems to be a Guillain-Barré syndrome of unknown origin. The fact that the polyradiculoneuritic symptoms started immediately after an upper respiratory tract infection and had an apparently good prognosis, was in favour of this diagnosis. So were also the results obtained by the performance of the normomastix reaction in the spinal fluid (fig. 2).

A lowering of the normomastix curve initially to the left, shifting more to the right later on, has repeatedly been observed in patients with the Guillain-Barré syndrome in the Department of Neurology, Oslo University Hospital (*Geelmuyden* 1955). Some authors (*Peters & Scheid* 1938, *Haymaker & Kernohan* 1949) have especially stressed the lowering of the curve to the right, as in intraspinal block, in cases with the Guillain-Barré syndrome.

The presence of central nervous system involvement would, however, according to the older concept of the Guillain-Barré syndrome, exclude such a diagnosis. Cerebral and spinal involvement was, indeed, very outstanding in this case, manifesting itself by the following symptoms and signs: Aphasia, somnolence shifting to insomnia, non-spontaneous behaviour, marked abnormalities in EEG, fluctuations in pulse and blood-pressure, extensor response of the plantar reflex on the right side, fasciculations, and epileptic seizures.

Fasciculations according to *Haymaker & Kernohan* (1949) are very rare in the Guillain-Barré syndrome, in contrast to the reports of many others (*Goebel* 1898, *Adler & Hoff* 1929, *Guillain* 1936, *Hagen & Baker* 1953). In our case they were very widespread, and presence of lesions of anterior horn cells was also revealed by the electromyographic examination.

Still rarer in the Guillain-Barré syndrome are epileptic seizures. However, *Russell & Moore* reported one case in 1943. This is very compatible with the fact that EEG is mostly found to be normal. This observation has especially been stressed in reports of cases with papilledema (*Ford & Walsh* 1943, *Krohn* 1952). EEG in our case showed marked abnormalities (fig. 1), as did EEG in a case reported by *Casamajor & Alpert* (1941). Recently *Giroire* & others (1955) demonstrated abnormal EEG in patients with the Guillain-Barré syndrome, but stressed the rarity of this finding and the need for further observations.

Even if the presence of spinal and cerebral symptoms and signs might be an objection to the diagnosis of the Guillain-Barré syndrome in a case like this, a more likely conclusion would be that in some cases of polyradiculoneuritis, the pathological process may also affect the central nervous system. This would support the view held by many authors that a wider concept of the term of Guillain-Barré syndrome is necessary (*Adler & Hoff* 1929, *Polan & Baker* 1942, *Haymaker & Kernohan* 1949, *Stanton* & others 1953). This wider concept would place the Guillain-Barré syndrome in a larger clinical entity, to which may belong certain types of encephalomyelitis, and certain peripheral radiculitides and neuritides (*Stanton* & others 1953, *Berglund* 1954).

If there is no respiratory failure, the prognosis in the Guillain-Barré syndrome is generally held to be good, although residual symptoms may be seen (*Peters & Scheid* 1938). In our case phychological tests and pneumoencephalography revealed signs of permanent damage to the brain, thus indicating that the psychical recovery was not so good as the physical one. The prognosis in cases with marked central nervous system involvement, therefore, should be considered with greater scepticism than in cases with pure polyradiculoneuritis.

A most noteworthy feature in this case are the changes of the patient's clinical condition, of the EEG and of the protein contents in the spinal fluid, appearing immediately after the start of corticotropin treatment (fig. 5).

Favourable results with corticotropin treatment are recorded in many publications (*Stillman & Ganong* 1952, *Blood & Locke* 1953, *Esseller & Kopp* 1954). Others, among them *Guillain* (1953), find no reason for treating such cases with corticotropin, because they will not admit an allergic etiology to be an important factor in the Guillain-Barré syndrome. The most reasonable explanation of the facts demonstrated by fig. 5 might be an influence by corticotropin on some patho-

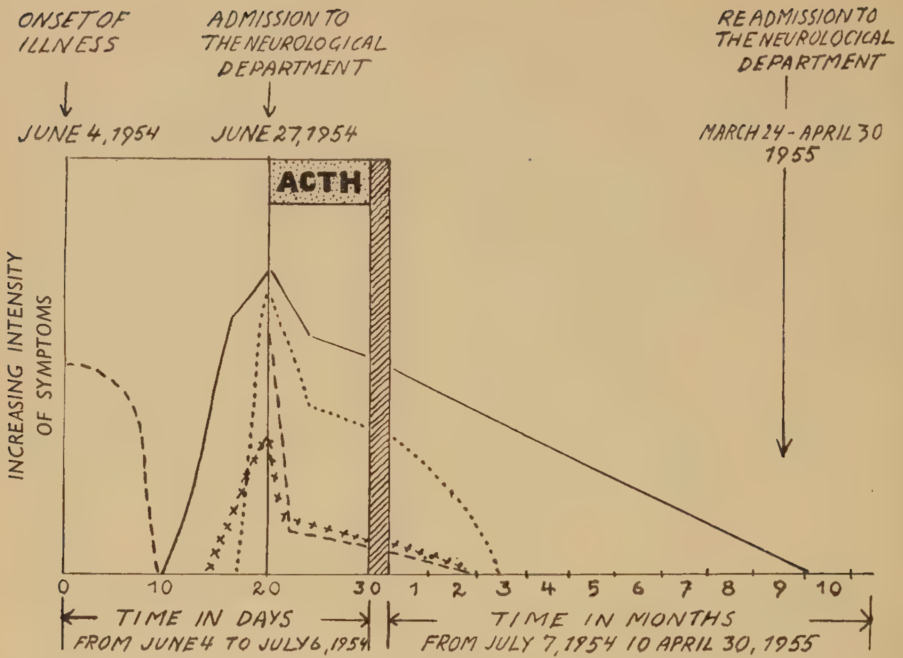

Fig. 5.

Case of the Guillain-Barré syndrome. The illness started with upper respiratory tract infection (indicated by – – – –), followed by polyradiculoneuritis (indicated by ———), and later by cerebral and spinal symptoms and signs (indicated by · · · · ·). ACTH (corticotropin) was given for ten days in 50 mg. daily doses from June 27, 1954. Post or propter an immediate change of the patient's clinical condition, and at the same time a reduction of EEG-abnormalities (indicated by – – – –) and of the protein contents of the spinal fluid (indicated by x x x x).

genetic factor, e.g. edema, but not on the underlying cause of the disease.

When bleedings for the first time occurred in this case, they were thought to be caused by the cortocotropin treatment. But no gastrointestinal illness was present beforehand, and no ulcer could be demonstrated, neither could free fluid in the peritoneal cavity nor occult bleeding in the faeces. The source of the bleedings apparently had to be sought in the retroperitoneal space. In the available literature the present author could find no previous records of retroperitoneal bleedings in the Guillain-Barré syndrome, not even in cases with visceral complications (*Sabin & Aring* 1941, *Vaughan* & others 1946, *Parker & Adams* 1947). *Gray & MacDonald* (1955) report acute abdominal illness to be extremely rare in the Guillain-Barré syndrome, but do not especially mention intra-abdominal bleedings.

Retroperitoneal hemorrhage, if not traumatic in origin, is most often secondary to a liver, kidney, blood, or arterial disease. In some cases, however, retroperitoneal bleedings may occur without any obvious reason (*Sachs & Macht* 1952). The very interesting question now arises if such bleedings may be caused by disturbances in autonomic centres, as may gastro-intestinal hemorrhage (*Cushing* 1932). The role of the hypothalamus in such hemorrhage has clearly been demonstrated by *French* & others (1952). Diencephalic disturbances may be seen in cases with the Guillain-Barré syndrome (*Guillain* 1953). In our patient they were very marked. The bleedings occurred only at a time when these disturbances were present. A possible connection between the retroperitoneal bleedings and the diencephalic involvement may therefore be suggested.

SUMMARY

The author reports a case of the Guillain-Barré syndrome with marked cerebral and spinal involvement. Marked abnormalities in EEG were present on the height of the illness, when the cerebral symptoms were most prominent.

Because of the patient's serious condition with respiratory troubles treatment with corticotropin was tried. An immediate clinical improvement simultaneous with normalization of EEG was observed.

On admission the normomastix curve showed a lowering to the left. But later on a lowering to the right was observed, as in cases with intraspinal block.

Retroperitoneal bleedings occurred at a time when diencephalic involvement was present. The possibility of a diencephalic origin of the bleedings is suggested.

The presence of central nervous system involvement in a case of polyradiculoneuritis seems to the author to be in favour of the view that a wider concept of the Guillain-Barré syndrome is necessary.

In the case presented the physical recovery seemed to be complete, but three epileptic seizures had occurred and psychological tests and pneumoencephalography revealed signs of permanent damage to the brain.

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THE NATURE OF BILATERAL AND SYNCHRONOUS CEREBRAL SPIKING

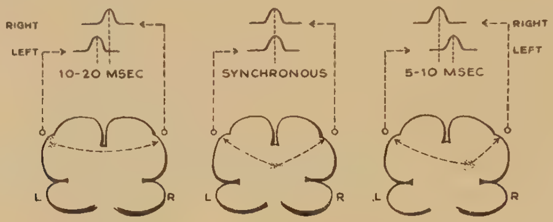
By

T. E. Ogden, R. B. Aird and B. C. Garoutte

Recent studies on the degree of synchronism of the electrical activity of the two cerebral hemispheres have thrown new light on the pacemaker mechanism of the brain stem which controls brain-wave activity. The precise timing of brain waves recorded from homologous scalp areas gives promise of contributing to our knowledge of the functional integration of cerebral activity in both normal and abnormal neurophysiologic processes. Our interest in this subject was initially stimulated by the common observation that bilateral and generalized dysrhythmias are found in the electroencephalograms of patients with unilateral pathology and that gross focal dysrhythmias, associated with unilateral pathology, frequently show a secondary focus involving the corresponding contralateral homologous areas. In such cases bilateral spiking may occur which appears synchronous when recorded with the usual inkwriters used in electroencephalography at the rate of 3 cm per second.

From the earlier studies by Curtis and others (1–6) on the transmission of electrical shocks and strychnine spikes by way of the corpus callosum to contralateral homologous areas in experimental animals, it seemed reasonable to suppose that this might be the pathway involved in the transmission of focal electroencephalographic abnormalities to homologous regions of the opposite (non-pathological) hemisphere. If this were true, the degree of lag or asynchronism of bilateral, homologous spiking (or other abnormal activity that could be followed by high-speed recording technics) might be used as an index of the depth of the lesion (as suggested in the theoretical diagram shown in Figure 1). Since this concept was presented in lectures delivered in

Sweden by one of us (R. B. A.) in 1953 at the invitation of the Swedish Medical Board, it seems appropriate that the results of our studies, which proved to be quite different from those anticipated, be published in a Scandinavian neurological journal.



I
CORTICAL
LESION

II
MIDLINE
LESION

III
SUBCORTICAL
LESION

Fig. 1.

Transmission of spikes from cortical and subcortical lesions showing the time relationships for each when recorded from homologous areas. This has since been shown not to account for all observed data.

MATERIAL AND METHODS

The studies were conducted with the aid of a Dumont double-beam cathode ray oscilloscope with attached Fairchild camera (35 mm). When recording at the rate of 50 cm/sec. it was readily possible to detect time differences of as little as one or two milliseconds. All the recordings were taken simultaneously from bilaterally symmetrical homologous areas of the scalp. Preliminary studies demonstrated that distinct waves with sharply defined peaks, such as electroencephalographic spikes, could be very satisfactorily studied by this rapid photographic method.

Because it was usually difficult to be certain of the exact point where a spiking potential left the base line, all measurements reported herein were referred to the peak of the spike, whether negative or positive. This usually could be localized with an accuracy of plus-or-minus one millisecond or better.

Nine patients were selected, who on previous electroencephalographic study had shown a gross focal dysrhythmia associated with a secondary focus in the opposite homologous area and with bilateral spiking activity that could be studied as described above. The initial electroencephalographic study was obtained with an 8-channel Grass EEG apparatus and with our standard technic (7) involving 18-electrode placements and all possible combinations of both scalp-to-ear and scalp-to-scalp recording.

In six of these patients there was definite clinical evidence to substantiate unilateral pathology with surgical confirmation in two instances. Post-mortem examination of the brain was done in one instance (J. P.). At autopsy definite unilateral pathology was found, without significant pathology in the contralateral cerebral cortex.

A second group of 18 patients was selected who showed on their initial electroencephalograms biliteral wave-and-spike activity either of the type usually seen in petit mal or of the petit mal variant type. Four of this group showed clinical or electroencephalographic evidence of focal pathology.

RESULTS

A. *Patients with gross focal dysrhythmias*

All nine patients with a gross, unilateral electrographic focus by the paper-recording technic frequently showed synchronous homologous spiking by the rapid photographic method. This spiking, however, was consistently synchronous in only one instance. Another showed spikes that were essentially synchronous, and all but one of the remainder showed perfect synchrony about 50 % of the time. In the last case, about 80 % of the spikes were asynchronous. It is of some further interest that the patient (J. P.) with definite unilateral pathology, as proven at autopsy, showed a high percentage of synchronous spiking.

Since six of these patients showed a high incidence of synchronous spiking and in two of these almost all the spikes were synchronous, it may be concluded that bilateral synchronous spiking associated with unilateral pathology is transmited, at least in a high percentage of the patients studied, by a different mechanism from the transmitted spikes studied by Curtis and others (1–6) in animal experiments. The synchrony found in our patients appears to require that a central pacemaker be postulated in these cases

The findings in the patient mentioned above (J. P.), where post-mortem studies were done, will be reported in more detail, since the unique features in this case not only illustrate the phenomenon of bilateral synchronous spiking in a patient with essentially unilateral pathology, but also suggest that such spiking is controlled by some centrally located subcortical pacemaker, which in turn may be influenced or triggered by impulses from a cortical "irritative focus" associated with the unilateral pathology.

CASE HISTORY

J.P. (UC Unit No. 196578).

Aggressive behavior disturbances, grand mal convulsions, and confusional episodes had characterized the patient's life course from the age of 15 months. There was no history of birth trauma or infection. A large, left-sided cerebral cyst was reported to have been removed at another hospital at the age of three years.

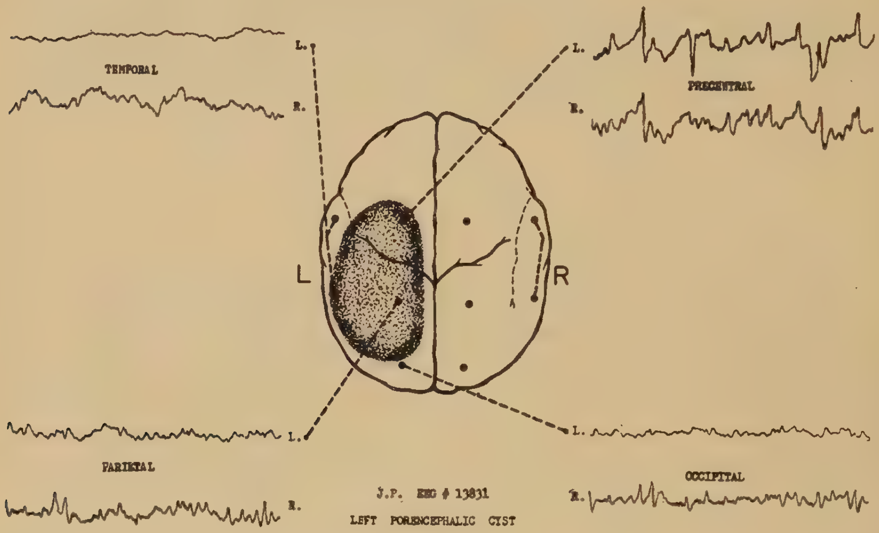


Fig. 2.

Electroencephalographic scalp recording before hemispherectomy in case J. P.

Examination on admission, when the patient was six years of age, showed a right-sided hemiparesis, with increased muscle stretch reflexes and an abnormal plantar response on the right, and borderline intelligence.

A ventriculogram showed a large porencephalic cyst of the left hemisphere.

Routine pre-operative electroencephalograms showed a marked generalized dysrhythmia plus left-sided flattening of the record from scalp areas overlying the cyst. There were also marked focal changes in the precentral area on the left where irregular waves and spiking activity of consistently high voltages were found. In addition, spiking of lower voltage was found in the homologous right precentral region. With the paper recording technic, these spikes appeared to be synchronous with those in the left precentral region (Fig. 2).

Oscilloscopic studies before surgery showed that many of the spikes recorded bilaterally from the precentral regions were perfectly synchronous. It is worth emphasizing that even at a film speed where a difference in timing of two milliseconds was easily detectable, there remained no question about this synchrony (Fig. 3).

At surgery[1], a large porencephalic cyst, involving most of the left hemisphere, was found. The entire cortex on the left was removed surgically, with the exception of a small portion of the left hippocampus.

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[1] Performed by Dr. E. B. Boldrey, Associate Professor of Neurological Surgery.

Electrocorticography at the time of surgery was done with an 8-channel Grass EEG apparatus utilizing ink writers with a paper speed of 3 cm. per sec. By this technic the precentral spiking on the left appeared synchronous with extremely high-voltage spikes coming from the posterior portion of the floor of the porencephalic cyst. This point of recording was directly over the left thalamus. It was concluded from the electrocorticography that the synchronous spiking in both cortices was probably reflected from the region of this deep focus.

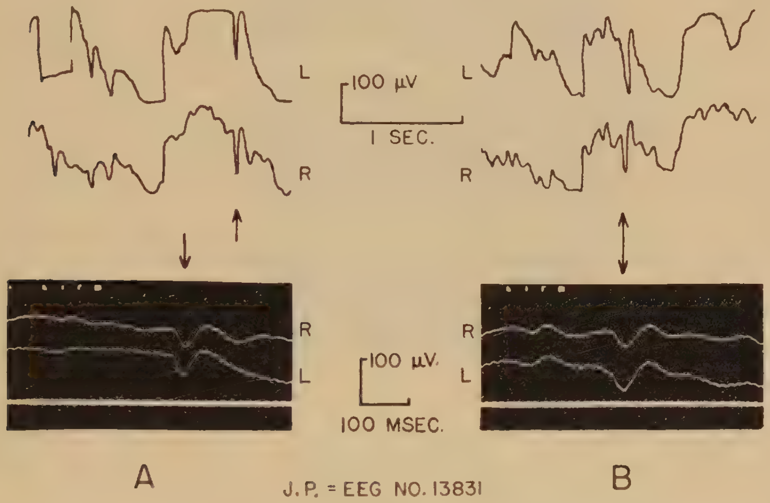

Fig. 3.

Simultaneous paper recording at 3 centimeters per second and photographic recording at 12.5 centimeters per second of two spikes from the right and left precentral leads in case J. P.

A. The left-sided spike preceded the right-sided spike by about 10 milliseconds.
B. The spikes from right and left sides were synchronous.

Postoperatively, the right hemiparesis was exaggerated, but the child's behavior was improved—he was less aggressive, less hyperactive, and more sociable.

A postoperative EEG record showed a complete absence of all spikes over the right cerebral hemisphere as well as the left where the pathological cortex had been resected. It should also be noted that this was true even though the thalamic area in the floor of the cyst, which by electrocorticography appeared near the site of origin of the large spikes, had not been disturbed at the time of surgery and was left intact.

Six months after surgery he was re-admitted because of signs of increasing intracranial pressure. Choroid plexectomy and Torkildson procedures were done. He died suddenly seven months after surgery.

Autopsy showed (1) the left hemispherectomy; (2) bilateral status marmoratus of the basal ganglia which was most severe on the left side; (3) atrophy of the corpus callosum; (4) chronic granular ependymitis with closure of the cerebral aqueduct and a superimposed hydrocephalus; and (5) an atrophic left pyramidal tract.

Comment: In view of the synchronous spiking in the homologous precentral areas, it appeared that the spiking must be controlled by a pacemaker in some central thalamic or brain-stem region. It was felt that the high-voltage spiking found over the left thalamic region at operation may have been near the source of the bilateral synchronous spiking in this case. Also, since all spiking ceased following resection of the pathological left cortex, it appeared that the deep central source of spiking must have been triggered by the abnormal influence of the left pathological cortex. This result thus supports the possibility of central nuclear excitation by unilateral lesions.

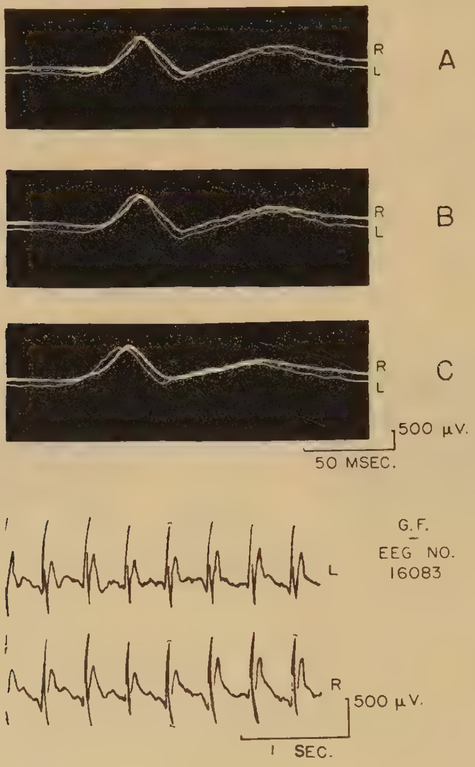

Fig. 4.

Simultaneous paper recording at 3 centimeters per second and photographic recording at 50 centimeters per second of successive spikes during a petit mal spell, patient G. F. (Frontal-Precentral scalp-to-scalp leads).

A. Right-sided spike about 1 millisecond behind left-sided spike.
B. Right-sided spike about 3 milliseconds behind left.
C. Right-sided spike about 6 milliseconds behind left.

B. *Patients with bilateral wave-and-spike discharge*

The unexpected observation on oscilloscopic study that all of the patients with unilateral focal dysrhythmias showed bilateral spiking, which was either synchronous or essentially so, suggested that the mechanism involved might be similar to that obtaining in the bilateral wave-and-spike discharge of petit mal. Correspondingly, 18 patients with petit mal or petit mal variant discharges were next studied by the oscilloscopic technic.

The percentage of perfectly synchronous spikes in patients with bilateral wave-and-spike discharges varied widely from only a few per cent to approximately 50 per cent. In all patients the asynchrony varied with time (Fig. 4), occasionally in a somewhat rhythmical fashion. The asynchrony rarely exceeded 20 milliseconds, and usually was not lateralized, i.e., the spikes at times led on one side, at times on the other. In four patients the leading spikes were always on the same side.

DISCUSSION

The bilateral synchronous spiking which was obtained in all of the patients with gross focal dysrhythmias and with presumably unilateral pathology must be different from the transmitted strychnine spikes, as studied by Curtis and others (1–6) in their animal work. It would appear that the pacemaker for this form of spiking must be centrally located, as Jasper and Penfield on the basis of ordinary EEG recording have suggested in the case of bilateral metrazol spikes (8). However, aside from the type of evidence reported in our operative case, it is impossible to assign the pacemaker to a thalamic center as opposed to a lower center in the brain stem. In our operative case the bilateral spiking frequently was synchronous to within one millisecond. From this it would appear that the pacemaker for the spiking must be almost precisely in the midline. Since the floor of the cyst was slightly to the left of the midline, the spikes noted there must have been controlled by the central pacemaker rather than being the source of the bilaterally synchronous spiking. If this is correct, a deeper thalamic, hypothalamic or brain stem pacemaker must be postulated in our operative case.

Although there is considerable experimental evidence in the older literature to suggest that the thalamus may be involved in bilateral spiking (9–14) it is well known that the massa intermedia, which has been shown in animal experiments (Jasper and Doogleever-Fortuyn, 1947) (15) to provide a connection across the midline in the feline thalamus, is not present in about 30 % of human brains. Since bilaterally synchronous spiking was found in some measure in all of our patients with gross focal dysrhythmias associated with unilateral pathology, it appeared unlikely that the thalamus could be either the primary source of such bilateral spiking or the center in which the pacemaker was located. A lower brain stem location, therefore, seems likely.

The asynchronous spiking in a high percentage of our patients with bilateral wave-and-spike discharge supports the recent observations of Cohn (16), who found the spiking of petit mal to be largely asynchronous in 100 patients. Although this might tie in with the fact that the bulk of the thalamus is lateral to the midline, as already stated, our observation of a considerable percentage of perfect synchrony in nearly all patients suggests a lower sub-cortical center for the pacemaker mechanism. Regardless of the actual anatomical location of the pacemaker, the *variations* in the degree of asynchronism would appear to necessitate a more dynamic concept of the pacemaker mechanism, one compounded of reverberating circuits or other neuronal systems capable of producing a shifting asynchronism. The variations of the degree of asynchronism noted in our patients, and especially in those where leading on one side shifted to leading on the other, constitutes strong evidence in favor of a paramesial pacemaker mechanism.

Since our evidence strongly implicates a similar regulatory mechanism for the bilateral spiking associated with both unilateral pathology and petit mal, the possibility is raised that all types of bilateral synchronous spiking may have a common paramesial pacemaker.

It should be emphasized that our data, both for focal dysrhythmias and the diffuse wave-spike activity of petit mal, are concerned with the pacemaker mechanism synchronizing cerebral activity and do not afford information on the primary source of spiking. The latter conceivably may be well off the midline and either subcortical or cortical in location (Hayne, Belinson and Gibbs, 1949 (17); and Bickford, Keith and MacCarty, 1955 (18)).

In the patients with unilateral cortical pathology the possibility was suggested that a stream of abnormal impulses from the lesion may affect the physiological state of the paramesial regulating mechanism (see the finely dashed lines of Fig. 5). Since the focal pathology in our group of patients varied widely in location, however, no specific pathway (such as suggested by the bilaterally symmetrical heavy dashed lines of Fig. 5) or center can be implicated in these cases. It would appear from this that the paramesial pacemaker mechanism must have diffuse connections with the cortex. This immediately brings to mind the diffuse thalamocortical projection system, or more likely for the reasons given, the ascending reticular activating system with its known diffuse projection to the cortex of both sides.

There is also the possibility that focal lesions might have a comparable effect in the bilateral wave-and-spike discharge of petit mal. This, indeed, has been suggested by the findings reported in a patient by Penfield and Jasper (1947) (19). They found a generalized dysrhythmia with suggestive wave-and-spike activity in a patient with a right frontal lesion. Recording by the usual ink-writing technic, they found that the right frontal spikes preceded the bilateral spikes of the generalized dysrhythmia by 60 to 70 milliseconds. All spikes ceased after the lesion was excised. In this case, therefore, they felt that a diencephalic center of spiking was probably triggered by the cortical lesion.

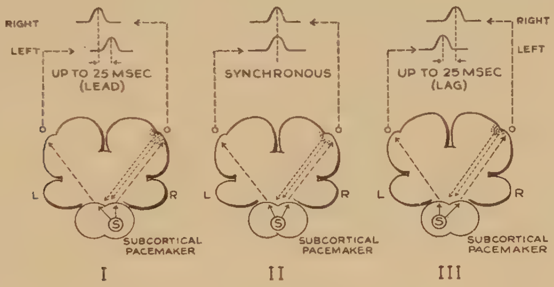

Fig. 5.

Hypothetical representation of the pacemaker mechanism. The encircled (S) represents the primary 'source' of the spiking potentials. The solid arrows leading from (S) represent transmission within the subcortical center, while the heavy dash-line arrows represent the bilateral projection of spikes to the cortex. The lighter dash-line arrows indicate the possible influence of cortical lesions (stippled) on paramesial subcortical structures.

A similar influence of focal pathology on the pacemaker of petit mal was also suggested by one of our patients (V. V.). This patient clinically exhibited typical petit mal spells and on occasion left adversive or Jacksonian seizures. By electroencephalography the patient showed the usual generalized three per second wave-and-spike activity. In addition, an electrographic focus of slow activity appeared in the right temporal and central areas. In a high percentage of runs the wave-and-spike discharge was noted to start on the right side one or two seconds before the left. Oscilloscopic study with rapid recording, however, demonstrated that during the period of bilateral spiking, the spikes appeared to lead almost as often on the normal as on the presumably pathological side, with delays up to 20 milliseconds.

Without further studies, it cannot be decided whether this case was comparable with that reported by Penfield and Jasper (19). Nevertheless, in view of their findings and the findings in this case, the possibility that focal pathology may exert an important influence on the paramesial pacemaker of petit mal must be kept in mind.

CONCLUSIONS

(1) A study of the degree of synchronism of the brain waves of the two cerebral hemispheres has been undertaken with the aid of high-speed recording technics capable of detecting differences of homologous spiking of as little as one or two milliseconds, in the hope of obtaining critical information on the pacemaker mechanism of the brain stem controlling the synchronization of cerebral activity.

(2) Nine patients with gross, unilateral, EEG foci showed synchronous homologous spiking by oscilloscopic recording. Since six of these patients showed a marked degree of synchronous "spiking", in two of whom the incidence of synchrony approached 100 %, it was concluded that bilateral synchronous spiking associated with unilateral pathology was not transmitted via the corpus callosum, as previously had been shown to be the case in experimental studies with electrical stimulation and strychnine spikes. The evidence for a central pacemaker in the brain stem is presented.

(3) Electrographic recording at operation from the thalamic region in the floor of a huge porencephalic cyst of a child who previously had shown bilateral synchronous spiking by oscilloscopic study, afforded further evidence for a central pacemaker mechanism, probably located in the brain stem. Also, since all spiking ceased following resection of the pathological left cortex, it appeared that the deep central source of spiking must be triggered by the abnormal influence of the pathological cortex. This result and other evidence is presented in support of the concept of central nuclear excitation by unilateral lesions. Since the focal processes in our patients varied widely in location, no specific pathway or center can be implicated. This lack of specificity suggestively implicates the ascending reticular activating systems with their known diffuse projections to the cortex of both sides.

(4) Eighteen petit mal patients with bilateral wave-and-spike discharge showed variable degrees of asynchrony ranging up to about 20 milliseconds. In several instances the asynchronism shifted across the midline with alternate leading on one and again on the other side. Although a central or paramesial pacemaker mechanism for the wave-and-spike discharge seems likely, the actual source or sources of the discharge appeared to be off-center in most instances. This, in addi-

tion to the variable patterns of asynchronism found, indicates the necessity of a more dynamic concept of the pacemaker in petit mal—one compounded of reverberating circuits or other active neuronal processes capable of producing a shifting asynchronism.

(5) The similarity of the regulatory mechanism for both the bilateral spiking associated with unilateral pathology and the bilateral spiking of petit mal suggests that bilateral synchronous spiking of all types may have a common paramesial pacemaker. Certain evidence is reviewed that supports the possibility of central nuclear excitation by unilateral lesions in patients with petit mal as well as in convulsive disorders associated with unilateral cortical pathology.

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NATURAL HISTORY AND EVOLUTION OF THE CONCEPT OF SCHILDER'S DIFFUSE SCLEROSIS

By

CHARLES M. POSER[1] and LUDO VAN BOGAERT

INTRODUCTION

> "Die diffuse Sklerose des Gehirns ist ein Sammelbegriff der heterogene Krankheitsformen umfasst."
>
> *Max Bielschowsky*, 1928.

The nosological situation of the various disease entities which are commonly grouped under the eponymic designation "Schilder's disease" or "diffuse sclerosis" has scarcely changed since Bielschowsky made his apt remark about them almost three decades ago.

It was Strümpell who first used the expression "diffuse sclerosis" in 1879 to describe the hard texture of the freshly removed brain of a chronic alcoholic. Schmaus, in 1888, again used the term to describe the macroscopic appearance of the brain of a 21-month-old child who had died after an illness lasting a year which was characterized by psychic troubles, fever, epileptic seizures, and generalized contractures. In 1897 Heubner used the phrase to describe cerebral sclerosis which extended beyond or bore no relation to focal lesions of a vascular, infectious, or neoplastic nature and which were almost always surrounded by small areas of glial sclerosis.

The term "encephalitis periaxialis diffusa," with which Schilder was to characterize his three cases of "diffuse sclerosis" in which the axonal-myelin sheath dissociation resulted in a periaxial process, had already been suggested in 1906 by Marburg in reporting a case of acute multiple sclerosis which he called "encephalomyelitis periaxialis sclero-

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ticans." This concept of a periaxial destructive process had been mentioned in 1880 by Gombault and in 1903 by Stransky in their studies of "discontinuous involvement" in polyneuritides. It remained for Schilder, however, to describe "diffuse sclerosis" as it is known today and to differentiate it according to the concept of Heubner from the other incompletely characterized conditions that resulted in diffuse glial overgrowth of the cerebral hemispheres.

Schilder's first case, published in 1912, was that of a 14-year-old girl who presented signs of mental deterioration associated with evidence of increased intracranial pressure and was diagnosed as suffering from a posterior fossa mass lesion. The disease lasted four and a half months. Histological examination of the brain revealed extensive bilateral demyelinization with almost complete sparing of the axons and the subcortical U-fibers. The areas of demyelinization had a sharply demarcated border. Within those areas there was a marked glial reaction with a large number of neutral fat-laden phagocytes.

From this case Schilder drew the following conclusion: There is a diffuse disease of the white matter of the brain in young children which from the macro- and micro-pathological findings would appear to be a new entity. Because of the relative sparing of the axons, he proposed the name "encephalitis periaxialis diffusa." The clinical picture of this disease is extremely variable. It may present at times under the guise of a cerebral neoplasm, at other times it will mimic multiple sclerosis, and on still other occasions it will simulate a "diffuse sclerosis" as defined by Heubner. The diagnosis can be suspected only when the neurological signs suggest widespread involvement of the cerebral hemispheres. Cases of what seem to be rapidly progressing multiple sclerosis in children should also suggest the diagnosis of this disease. The disease is fatal and there are but few remissions during its course. From the pathological point of view the disease appears to be very close to multiple sclerosis, especially to its acute form.

A year later, in 1913, Schilder had occasion to publish the results of a thorough study he had made on the brain of a case previously described by Haberfeld and Spieler in 1910. He included this case in his newly established category of "encephalitis periaxialis diffusa." The most significant point in the clinical history of this child was that the family stated that another child had previously died of a similar illness. The fact that the disease might be familial seemed of little importance to Schilder, however, since there had been several published reports of familial cases of multiple sclerosis as well as the reported cases of another familial type of "diffuse sclerosis," the Pelizaeus-Merzbacher type.

Many cases of "diffuse sclerosis" or "Schilder's disease" were reported during the following years, but in 1924 Schilder published the last of his three cases. The report concerned a 37-year-old woman who, a month after a bout of what had been called influenza with complete remission, complained of severe headache, generalized weakness, and urinary incontinence. She was found on neurological examination to show minimal motor weakness, bilateral papilledema, and a curious apraxia of lid movements. She died following a negative surgical exploration.

Pathological examination revealed extensive areas of demyelinization of a diffuse type without sharply demarcated borders. The demyelinated areas showed marked glial proliferation with, in certain places, enormous accumulations of neutral fat-containing phagocytes and many giant astrocytes. The most remarkable finding was that in many areas there were marked perivascular lymphocytic infiltrates as well as capillary proliferation. Certain regions of the cortex, even those far removed from lesions of the white matter, had this type of inflammatory reaction as well as fatty infiltrations in neurons and vessel walls. In areas in which the white matter showed little if any demyelinization, the myelin sheaths were pale, thinned out, or swollen. These areas also had an unexpectedly severe gliosis and phagocytosis. In discussing this case, Schilder emphasized the fact that in areas of the brain which showed no marked alterations of the parenchyma, inflammatory reactions could be found around the small blood vessels.

Schilder also stressed the lymphocytic character of these perivascular cuffs and the fact that the entire white matter was involved. He felt that there were both inflammatory and degenerative features in the disease process but believed that it should be classified primarily as an inflammatory process. He concluded that this case was a diffuse subacute encephalitis which belonged to the group of periaxial encephalitides and must be placed among the leucoencephalitides. He went on to differentiate it from the epidemic encephalitides, in which the gray matter is mainly involved, as well as from multiple sclerosis, because here there appeared to be one main focus and because areas usually involved in multiple sclerosis such as the pons and the cerebellum were not damaged.

There is little doubt that the pathological features of this case are greatly different from the other two described by Schilder. In 1951 Lumsden pointed out the similarity between the picture in Schilder's third case and the one described by van Bogaert and De Busscher in 1939 and van Bogaert in 1945 as a case of "subacute sclerosing leucoencephalitis." Although it is not certain that Schilder's third case does belong to this particular type, it is probable that it was some type of subacute encephalitis.

Unfortunately, following Schilder's example, many subsequent authors gave the name "Schilder's disease" or "diffuse sclerosis" to a host of unrelated and heterogeneous disease entities which have become recognized lately as belonging to entirely different categories. British and American authors in particular have tended to retain all these superficially similar diseases under the name "Schilder's disease" allowing only for a few subgroups. Thus Adams and Kubik in 1950 included only two types under the heading "Cerebral Sclerosis of the Demyelinative Type": Schilder's "encephalitis periaxialis diffusa" and the metachromatic leucoencephalopathies.

However, as far back as 1921 Neubürger had proposed a classification based on the presence or absence of so-called inflammatory or neoplastic reactions and enumerated three types: the inflammatory, the degenerative, and the glioblastomatous types. Einarson and Neel, and later Strömgren, adopted this basic plan and stated that although they felt "diffuse sclerosis" should be considered a single disease entity, they recognized the following subgroups:

1. The glioblastomatous reactive type
2. The inflammatory reactive type
3. The sporadic degenerative type
    a) with metachromatic pre-lipoids
    b) with both fatty and metachromatic lipoids
4. The familial heredo-degenerative type.
    a) the acute infantile type of Krabbe
    b) the subacute type of Scholz
    c) the adult type of Ferraro
    d) the chronic type of Pelizaeus-Merzbacher

Finally, in separating the subacute encephalitides of children such as Dawson and van Bogaert had described from cases of "Schilder's disease," or, as he called it, "diffuse cerebral sclerosis of Schilder," Greenfield differentiated them in 1952 on the basis of the method of myelin catabolism and proposed the following classification:

1. The group in which myelin catabolism follows the ordinary lines seen in disseminated sclerosis, vascular softenings, and Wallerian degeneration with the accumulation of abundant sudanophilic lipid. The Pelizaeus-Merzbacher group is included here.
2. The group of metachromatic leucodystrophy, familial or sporadic, in which sudanophilic lipids are found only in the blood vessel walls or not at all, and there is accumulation of material with the reactions of galactolipid.
3. The smaller group characterized by the presence in areas of recent degeneration of clusters or packets of epithelioid or "globoid" cells.

The problem of classification has been further complicated by the fact that it is extremely difficult in many instances to differentiate on pathological grounds between diffuse demyelinization and sclerosis resulting from a so-called primary demyelinization and the results of vascular or toxic disease. Probably the best example of this is afforded by many French authors who call the "diffuse sclerosis" described by Schilder in 1912 *maladie de Schilder-Foix.*

In 1913, using the name *sclérose intra-cérébrale centrolobaire et symétrique,* Pierre Marie and Charles Foix reported the case of an 18-year-old tubercular girl who presented rather rapidly all the signs and symptoms of "diffuse sclerosis." She recovered from this episode with only minor sequelae. At her death ten years later from pulmonary tuberculosis, bilateral symmetrical areas of sclerosis were found involving the occipital lobes and exactly corresponding on close examination to the territory served by the posterior cerebral artery. In 1927 Charles Foix and Julien Marie republished that case and added two more cases. The latter two cases again were somewhat atypical and would fit better into the category of perinatal vascular encephalopathies. But in spite of Hallervorden's paper in 1932 in which he specifically pointed out in discussing Foix and Marie's cases that they were probably instances of sclerosis following vascular or anoxic injuries, and in spite of the subsequent work of Meyer and Cook, and Meyer and Jones on sclerosis in mental defectives and infantile encephalopathy, the eponym *maladie de Schilder-Foix* is still in vogue and still cases of perinatal encephalopathy are reported as instances of "Schilder's disease."

One of the most thorough monographs on the subject is the one written by Bouman in 1934. He collected 100 cases of "Schilder's disease" or "diffuse sclerosis" which he analyzed in detail. From this study he drew the conclusion that "diffuse sclerosis" was much more common in children since 50 of his cases were under the age of 16 while the other 50 ranged in age all the way up to 70. But close analysis of the cases used by Bouman in his computation reveal the following: Among the children's group, six cases were not autopsied, and in four instances the original paper could not be obtained in order to evaluate the diagnosis in the light of present knowledge. Of the remaining 40 cases, only 17 were found to be instances of "diffuse sclerosis" of the 1912 Schilder type, the rest consisting of 14 leucodystrophies, 5 perinatal encephalopathies, 2 probable subacute sclerosing leucoencephalitides, 1 diffuse glioblastomatosis and 1 perivenous encephalitis. Of the 50 adults, 35 proved to be cases of diffuse or diffuse-disseminated (transitional) sclerosis while the rest again consisted of a mixture of leucodystrophies, diffuse glioblastomatosis, perivenous encephalitides, etc.

The need for a clearer and more workable classification based on clinical and pathological evidence is an evident one. The leucodystrophies are very frequently familial and therefore a correct diagnosis must be obtained before advising the patient's family in regard to future offspring. Better understanding of these diseases coupled with new methods of investigation such as the bio- and histochemical ones will surely lead to better understanding of the demyelinating process. However, it would be dangerous to insist upon a detailed classification, even based on the best clinical observation and the most minute histological study, in the absence of a known etiological mechanism or agent. Such a classification can only be a step forward and not an end in itself.

The diseases under consideration have as a common characteristic diffuse demyelinization of the cerebral white matter. Our histological methods are far from perfect and it is worth remembering that the intact appearance of myelin as demonstrated by the common myelin-sheath stains does not necessarily mean that the myelin is chemically intact. There are undoubtedly certain chemical changes that may occur in myelin that cannot be detected by the staining methods we have available at this time.

Demyelinization, of course, is a completely nonspecific reaction of nervous tissue to any number of injurious agents (Scheinker). The role of "allergy" is not well known, yet some phenomena which are loosely spoken of as "allergic" may produce in the brain a pathological picture very similar to diffuse sclerosis; certain cerebro-toxins may also have the same effect (Ferraro, Verhaart). The way in which age, racial background, endocrine phenomena, previous exposure to neurogenic disease, or circulatory factors may affect the response of cerebral tissue to a given injury is still not clearly understood. It is therefore not illogical to assume that the same disease may represent itself in somewhat different forms in different individuals depending upon the interplay of the above-mentioned factors. On the other hand it is quite as conceivable that different diseases may have the same clinical picture and provoke similar pathological changes.

Even though classical pathological anatomy and histology would seem to have contributed as much as can be expected of them and the future appears to belong to electrical, histochemical and biochemical techniques, the basis of judgment established by the older methods must serve until etiological agents have been discovered or until the other techniques provide better criteria. There are already indications that biochemical studies of cerebral white matter in these diseases will offer just that.

As a basis for the differentiation of the group of diseases included under the eponym "Schilder's disease" we have chosen as prototypes the three cases originally reported by Schilder in 1912, 1913, and 1924.

The first group will thus consist of true diffuse sclerosis, which, to avoid confusion with terms formerly employed, will be referred to henceforth as *Schilder*'s *cerebral sclerosis.* The second group will consist of the truly degenerative (and probably heredo-degenerative) diseases of myelin, the *leucodystrophies,* while the third group will consist of the *subacute encephalitides* typified by van Bogaert's subacute sclerosing leucoencephalitis.

SCHILDER'S CEREBRAL SCLEROSIS

The term Schilder's cerebral sclerosis, to be abbreviated henceforth as S.C.S., has been adopted in order to designate what the authors consider to be the true "encephalitis periaxialis diffusa" as described by Schilder in 1912.

The relationship between this type of demyelinating disease and disseminated or multiple sclerosis has been the subject of several papers. Schilder himself considered the possibility that his type of "diffuse sclerosis" might be closely related to multiple sclerosis. As more cases of the disease were reported, it became evident that the criteria for differentiating between the two were less and less tenable. Indeed, it appeared that S.C.S. might be a different form of multiple sclerosis, perhaps in some way the result of a difference in the "terrain"; i.e., the cerebral tissue in which the disease process was occurring. Kufs suggested that the rarity of multiple sclerosis in and the apparent predilection of what was called "diffuse sclerosis" for childhood might result from the fact that the infantile organism is hypersensitive to the "infective agent." Thus the organism's reaction to the "virus" in the child is expressed by the more severe form of "diffuse sclerosis." Heernu, Martin and van Bogaert, and Roizin, Helfand and Moore also felt strongly that S.C.S. and disseminated sclerosis were slightly different manifestations of the same disease.

The apparent truth of this belief is enforced by the fact that there are indeed many cases of what have been called "diffuse sclerosis" in which isolated plaques of disseminated sclerosis can also be found. In a recent paper, one of us (CMP) has reviewed this question in some detail.

Briefly stated, it was found that out of 105 reported cases of S.C.S. only 33 belonged to the "bilocular" type; i.e., in which the only lesions present were bilateral symmetrical areas of demyelinization involving a large part of the centrum ovale. In 72 cases, on the other hand, there were several or many small isolated plaques as seen in classical disseminated sclerosis in addition to the large bilateral lesions. We have designated that type of case as *diffuse-disseminated,* or *transitional sclerosis.* Thus it would seem that the bilocular type of S.C.S. is rather infrequent while the cases of transition between it and multiple sclerosis are more common.

Of interest are the cases reported by Greenfield (1950) of a 53-year-old woman with diffuse myelitis and a large single demyelinating lesion of one occipital lobe, and by Stauffenberg of a 21-year-old woman who had bilocular cerebral sclerosis with an additional small single plaque in the chiasm. To complete the gamut of transitional cases between S.C.S., multiple sclerosis, and Devic's disease, or neuromyelitis optica, one should mention van Bogaert's case (1932) of a 31-year-old man who presented the classical symptoms of Devic's disease and at autopsy three years later was found to have had transitional sclerosis. Paarman reported a similar case and reviewed the subject more recently. Further details of the histopathological reasons for considering S.C.S. and multiple sclerosis manifestations of the same disease have been well covered in Lhermitte's monograph.

Age of onset

In view of the relative frequency of transitional sclerosis among cases reported as "diffuse sclerosis," it is interesting to re-examine the figures on the age of onset of "Schilder's disease." Most textbooks simply state that "Schilder's disease" occurs most frequently in childhood, while available published figures agree in general on the relative rarity of multiple sclerosis in childhood. The most recent statistics on the latter are those of Carter, Sciarra, and Merritt who, in addition to their own 46 autopsied cases, reviewed 1,107 cases from the literature. Only 2 per cent of the 1,153 cases of multiple sclerosis started before the age of 10. The data on our 33 cases of the bilocular form of S.C.S. (excluding cases of leucodystrophy, perinatal encephalopathy, leucoencephalitides, etc.) reveal that the disease started before the age of 10 in 45.5 per cent of the cases.

On the other hand, the figures for the age of onset in our 72 cases of transitional sclerosis follow a distribution curve which closely resembles that for multiple sclerosis as drawn from Carter, Sciarra, and

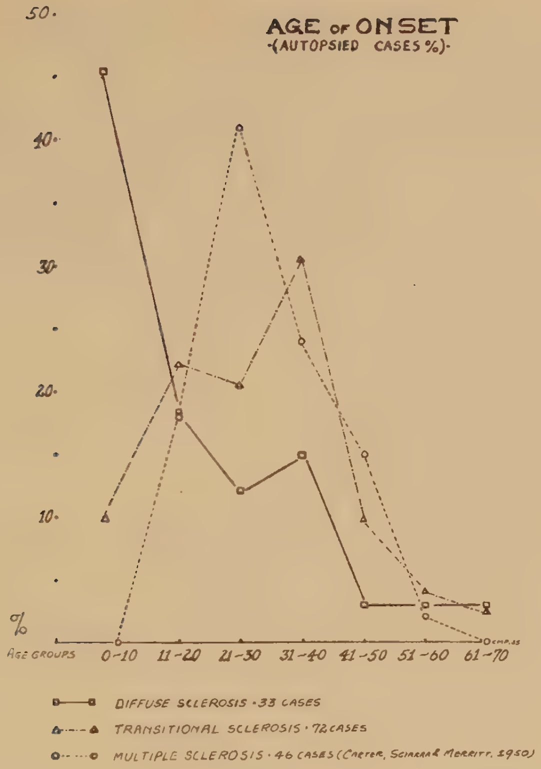

Fig. 1.
Comparison of age of onset by age groups of diffuse (bilocular), transitional and multiple sclerosis.

Merritt's 46 autopsied cases, except that the disease started before the age of 10 in none of their cases and in 9.8 per cent of the cases we had collected from the literature (see Figure 1). Only autopsied cases were used for that study. It would seem that in the younger age group there may be certain factors that result in symmetrical massive lesions rather than the multiple lesions more characteristic of later years.

Duration of the disease

It is frequently stated that "Schilder's disease" usually runs a subchronic course over a period of 2 or 3 years. We have analyzed the data on duration of the disease in the 33 cases of bilocular sclerosis and 72 cases of transitional sclerosis we had collected from the litterature.

In 29 cases of bilocular sclerosis for which there was information available regarding the duration of the disease, the mean duration was

3.2 years, with extremes ranging from 15 days (Casper) to 19 years (Junker) and 25 years (Einarson and Neel case IX). In 18 cases (62 per cent) the disease lasted one year or less.

In the group of 70 cases of transitional sclerosis for which this information was known, the mean duration was 6.2 years with extremes ranging from 3 days (Kornyey) and 9 days (Stewart, Greenfield and Blandy, case III) to 30 years (De Morsier and Feldmann) and 45 years (Bodechtel and Guttmann, 1932, case VII). Although the disease lasted one year or less in 28 cases (40 per cent), it lasted 10 years or more in 16 cases (23 per cent).

There seems to be no relationship between the age of onset and the duration of the disease.

Clinical picture

Because of the mixture of bilocular types with cases of transitional sclerosis, the clinical picture of S.C.S. as usually described offers many variations. Even among the bilocular type of S.C.S. the picture may differ considerably, to some extent depending on the age of the child and thus the degree of myelinization of his nervous system.

Lhermitte has divided the clinical picture of S.C.S. into several types:

1. The progressive form: psychic difficulties, pyramidal tract signs, blindness, and deafness are the most common symptoms; the disease is progressive but seems to go forward gradually.
2. The polysclerotic form: the disease progresses by successive bursts which are suggestive of classical multiple sclerosis.
3. The pseudo-tumoral form.
4. Type with predominant psychiatric symptoms: the mental picture may completely dominate a rather benign neurological examination and the psychiatric manifestations may run the whole range of dementias, manias, melancholia, and even schizophrenic episodes.

Lhermitte adds to this list progression followed by permanent remission, the form described by C. Foix and J. Marie, but there seems no valid reason for including this type of neurological disturbance in the group of S.C.S.

As a rule, bilocular sclerosis takes on the so-called progressive form with many instances of increased intracranial pressure suggesting a mass lesion, while the polysclerotic form, as its name indicates, is much more common in transitional sclerosis. In the adult, marked psychiatric manifestations are very frequent. Actually, the clinical picture is simply a manifestation of the extent of damage and involvement of the cerebral white matter, and it is for that reason extremely difficult if not impossible to differentiate clinically between the bilocular and the transitional forms of cerebral sclerosis and to separate these from the leucodystrophies in the absence of a positive family history. Further evidence regarding the relationship between S.C.S. and multiple sclerosis must await biochemical studies. The work of Yahr, Goldensohn and Kabat with cerebrospinal fluid determinations of gamma globulin will have to be extended to cases which were clinically diagnosed "diffuse sclerosis."

Histopathological findings

Pathologically, S.C.S. may be characterized as follows:

1. There is usually a bilateral focus of demyelinization of the centrum ovale of the cerebral hemispheres, in general not altogether symmetrical, most frequently involving the occipital lobes. If the lesions are sufficiently anterior, the corpus callosum serves as a "bridge" over which the lesion seems to extend to the other side. The borders of the lesion are sharply demarcated from the healthy tissue and the U-fibers are very often spared.
2. The axons are usually involved to some extent, but much less than the myelin sheaths, the most severe destruction being found mostly in areas where the process is older.
3. There is evidence of myelin disintegration and of transport of the Abbau products to the stage of sudanophilic neutral fats. The glial reaction is also the same as the one seen in almost any type of cerebral injury regardless of etiology. In addition, there is frequent formation of giant multinucleated or swollen astrocytes which may dominate the histological picture. In certain cases of long duration, the products of disintegration and the phagocytes may have completely disappeared.
4. The degree of perivascular reaction depends upon the stage of demyelinization that has been reached before death. In active, early demyelinization, severe perivascular cuffing with lymphocytes and phagocytes may be seen although these will have disappeared from older "burned-out" cases.
5. The gliosis may also be said to be anisomorphic in that the intensity of the process differs from place to place just as does the degree of demyelinization, which may vary from an area of total loss of myelin to the "shadow-plaques" or *Markschattenherde* in which there is only slight loss of myelin.
6. Very frequently the areas of demyelinization give the impression of having been formed by the coalescence of several small plaques,

some of which may be centered upon a small blood vessel. In certain cases of true S.C.S., especially in the acute cases, their appearance may be very similar to that seen in the more severe cases of perivenous encephalitis (e.g., Stewart, Greenfield and Blandy case III; Kornyey's case).

Relationship with the perivenous encephalitides

The post-exanthematous and post-vaccinal encephalitides have long been regarded as possible forerunners of the large, diffuse areas of demyelinization found in S.C.S. Although it is true that there are instances of autopsy-proven bilocular or transitional sclerosis which closely followed an exanthem (Gagel, after measles; Lauritzen and Lundholm, after what was diagnosed as influenza, for example), there are too many cases of well-documented post-exanthematous encephalomyelitis which recovered completely as well as many cases of that type which were examined post-mortem and in which the typical perivenous areas of demyelinization were found showing no tendency to coalescence. It is also true that the "allergic" factor which is invoked to explain the post-exanthematous or post-vaccinal encephalomyelitides has had experimental support (Hurst), but until recently it was not possible, at least on histopathological grounds, to apply the principle of its mechanism to the formation of lesions in multiple or "diffuse" sclerosis. A new and most interesting light has been cast upon this subject by the publication of a paper by Uchimura, Shiraki and Haruhara: They reported on 9 autopsied cases of encephalomyelitis following anti-rabic inoculations and found that the lesions were identical in all aspects with those of classical multiple sclerosis. The report is of especial significance since multiple sclerosis is said to be unknown among the Japanese, and this again raises the possibility of a specific factor, perhaps a racial one, affecting the cerebral substratum and its reaction to a particular type of injury.

It is perhaps of related interest that in certain types of intoxications the resulting cerebral lesions cannot be distinguished histopathologically from those of S.C.S. (Jervis and Kindwall's ergotamine intoxication, Verhaart's lead encephalopathy, etc.).

Relationship with acute disseminated encephalomyelitis

For many years, the relationship between multiple sclerosis and acute disseminated encephalomyelitis has been the subject of erudite papers and discussions. Various writers have considered acute disseminated encephalomyelitis a highly acute form of multiple sclerosis, either the only episode of the disease or the first. Many patients with this particular affection recover completely so that follow-up studies are of great value. Unfortunately, there are relatively few such studies available in the literature. In 1947 Thygesen reported that of 29 patients diagnosed as suffering from acute disseminated encephalomyelitis, seven were found, 8 to 15 years later, to have multiple sclerosis. In 1950, van Bogaert reported on 19 patients with clinical acute disseminated encephalomyelitis who had been observed between 1927 and 1932. Three of them died during the acute phase. Of these, two were examined post-mortem. One of them was indubitably a case of acute multiple sclerosis while in the other were found small perivascular areas of gliosis, typical of what is seen in the so-called perivenous encephalomyelitis, while nothing suggestive of multiple sclerosis could be seen. Four of the remaining 16 patients subsequently developed typical multiple sclerosis while the other 12 remained neurologically intact.

The problem perhaps is not completely solved by these two publications, but after reviewing the many other anatomic studies on cases of acute disseminated encephalomyelitis (see Lhermitte, p. 106), it would seem that although acute disseminated encephalomyelitis surely represents a purely clinical entity, certain of the cases are instances of acute multiple sclerosis, while the majority are cases of perivenous encephalomyelitis. The problem of Hurst's acute hemorrhagic leucoencephalitis is perhaps of the same nature, and some authors feel that it represents simply a hyperacute form of perivenous encephalomyelitis (MacArdle, van Bogaert and Lhermitte). The case of acute hemorrhagic leucoencephalitis complicating varicella which Lander reported would seem to support that theory. Russell is of the opinion that Hurst's acute hemorrhagic leucoencephalitis is indeed closely related to acute disseminated encephalomyelitis and that both are "allergic phenomena." However, the number of such cases is still too small to be able to draw definite conclusions.

The perinatal encephalopathies

Further lack of clarity in the classification of the various syndromes called "Schilder's disease" was caused by the introduction of an acute, regressive nonfatal form of "diffuse sclerosis" by the French authors under the name of *maladie de Schilder-Foix.* This is quite understandable when one considers the difficulty so frequently encountered in differentiating on histo-pathological grounds between perinatal encephalopathy of vascular or anoxic origin and S.C.S. The clinical history should give a clue, since it is most unusual for S.C.S. to start at birth, while cases of perinatal encephalopathy will usually manifest a marked retardation of psychomotor development from the start. In other cases, such as those of acute cerebral diplegia, which is usually a result of vascular disease, the clinical history may not be of as much help. Woolf has postulated that the sclerosis which is a characteristic finding in acute cerebral diplegia is the result of edema of the cerebral white matter.

It is not inconsistent, perhaps, to extend this concept to the cases of perinatal encephalopathy which are almost always based on vascular or anoxic difficulties. In addition to the sclerosis, in many of these cases, there may also be the characteristic areas of cystic degeneration which aid in differentiation from S.C.S. as does the fact that the sclerosis almost always is appreciably more severe than the demyelinization. Other signs of anoxic encephalopathy coupled with the very frequent neuronal involvement will also help in the differentiation. Meyer and Cook, Hallervorden, and recently Crome have published good examples of this type of cerebral sclerosis.

The problem of differentiation also extends to the leucodystrophies, since in certain instances they may be familial. Russell and Tallerman published two cases of this type under the title "Familial Progressive Diffuse Cerebral Sclerosis of Infants," but closer examination of the post-mortem findings in one case reveals that they were more probably dealing with a perinatal vascular encephalopathy.

Balo's disease

In certain cases of S.C.S., some of the areas of uneven demyelinization occasionally give a marbled or agate-slice effect. In 1928, Balo was struck by the macroscopically noticeable areas of concentric demyelination in the brain of a 23-year-old man who had died after an illness lasting only three months. He proposed the name "encephalitis periaxialis concentrica" for this variant of S.C.S. Since that time there have been six additional cases published under that name. However, it must be pointed out that in half of these cases, as well as in Balo's original case, there are other areas either of bilocular or disseminated sclerosis in addition to the striking areas of concentric demyelination, and that the concentric layering is no more than a local phenomenon in otherwise ordinary cases of S.C.S. or of transitional sclerosis. There are also seven more cases of S.C.S. in which such extensive concentric areas were described although the cases were not classified as Balo's disease. The same can be said about several cases of disseminated sclerosis in which some of the small plaques have this concentric appearance. Ule and Kraemer's recently published case is of interest since a large plaque of concentric demyelination occupied the whole of the pons in a case of multiple sclerosis. Behr's review of the cases of concentric sclerosis is probably the most recent.

Hallervorden and Spatz felt that the concentric rings of demyelinization alternating with bands of retained myelin might be compared to the so-called Liesegang rings obtained when a metallic colloid diffuses through gelatin, and they used the analogy to support the theory that there was a blood-borne myelinolytic agent. In 1952 Hallervorden compared those rings to the ones produced by the potato-X virus to support a virus etiology for the idiopathic demyelinating diseases. On the other hand Ferraro has reported observing similar areas of concentric demyelinization in experimentally produced encephalomyelopathy with potassium cyanide.

It would seem that what has been called Balo's disease is not a separate entity but rather represents a purely local phenomenon in certain cases of demyelinating diseases of the multiple sclerosis type.

Binswanger's disease

The name "progressive subcortical encephalitis" of Binswanger, who first described the disease in 1894, means a rather specific type of focally demyelinating disease the histopathological appearance of which may occasionally resemble that of S.C.S. For that reason it has sometimes been placed in the group of primary demyelinating diseases. In reality the basic process is arteriosclerosis of small subcortical cerebral arteries, which results in multiple perivascular areas of demyelinization that may at times coalesce to give an appearance of diffuse disease. Detailed examination, however, will always reveal the prominent arteriosclerotic vessel wall changes which are the primary etiological factors of the disease, as Nissl pointed out in 1919.

Van Bogaert has recently reported a family in which four of fourteen siblings were suffering from this malady which had been clinically diagnosed as Alzheimer's presenile dementia. Pathological examination revealed the true nature of the process. The histopathological picture was sufficiently typical to permit excluding the cases from the leucodystrophy group in spite of the fact that the disease was familial. It is interesting to note that the case reported by van Bogaert and Nyssen under the title "Late Type of Progressive Familial Leucodystrophy" was an example of the association between Binswanger's disease and a true leucodystrophy.

Relationship between S.C.S. and other diseases

There have been reports of association of S.C.S. and adrenal insufficiency: Pfister, as well as Siemerling and Creutzfeldt, reported cases in children, while Hampel reported a case in an adult. Even though it might be tempting to invoke endocrine disturbances as contributing factors in the etiology of demyelinating diseases, it seems more probable that the combination of diseases might be the result of coincidence. The same can probably be said of Casper's case, in which there was a severe diabetes. However, the diabetes may have contributed to the very rapid (fifteen-day) course of the demyelinating disease.

Similarly Christensen and Fog found disseminated Boeck's sarcoid without an intracranial lesion in their case of bilocular sclerosis in a 59-year-old man, and Balo discovered lesions of periarteritis nodosa in visceral arteries, but not in cerebral arteries, in a case of bilocular sclerosis.

Familial incidence of S.C.S.

It is the belief of the authors that S.C.S. is simply a slightly different manifestation of the process responsible for disseminated sclerosis, and that in the same group of demyelinating diseases should be placed cases of what are at present called Devic's and Balo's diseases. We also believe that this group of diseases results at least in part from exogenous factors, as opposed to the leucodystrophies, which may well be the result of endogenous disturbances.

Since there is mounting evidence that S.C.S. is closely related to disseminated sclerosis, and since there have been a number of reported cases of familial multiple sclerosis, one would expect to find some cases of bilocular or transitional sclerosis occurring in the same family. This expectation has not materialized, except in one instance: Polstorff reported in 1940 the autopsy-proven case of a 40-year-old woman with transitional sclerosis, and the same year Junker published his autopsy report on the 19-year-old daughter who had a bilocular sclerosis. These are the only autopsy-proven cases of familial incidence we have been able to discover.

Pratt, Compston and McAlpine, in their extensive review of the subject of the familial incidence of disseminated sclerosis, stated in 1951 that there have been at least 184 families reported in which more than one member was suffering or had died from the disease. They added to the review 33 families that they themselves had studied. Autopsy material in familial cases of multiple sclerosis, however, is still rare. Pratt et al. were able to examine post-mortem two sisters of a family (Family V) in which the mother and two other sisters had clinical evidence of multiple sclerosis. They also confirmed the diagnosis in another family (Family D) in one of a pair of siblings with multiple sclerosis.

Nayrac et al. in 1954 cited reports of multiple sclerosis in four families in which two autopsies had been performed in each family, and five instances in which only one post-mortem examination had been performed in each family.

THE LEUCODYSTROPHIES

General clinical characteristics

It is very difficult to give an overall clinical picture of leucodystrophy. It is almost impossible to make a purely clinical diagnosis of this disease unless there is a well-documented family history. The clinical characteristics resemble and are as varied as are those of S.C.S. It is to be remembered that they do not result from the specific histological changes, such as the presence of globoid cells or abnormal myelin Abbau material, but rather reflect the extent of the demyelinating and sclerotic processes, those in turn being dependent to a certain extent on the age of the patient, the duration of the illness, and other conditions.

A good summary of the clinical characteristics is that of Bertrand, Thieffry and Bargeton:

The initial symptoms usually consist of gait difficulties, either of the ataxic type or due to spasticity or for both reasons. Following this, or at the same time, various mental difficulties appear. Character disorders predominate: irritability, agitation, spasmodic crying or laughing. Very rapidly this is followed by apathy; the patient loses interest in his surroundings. The attention span is shortened and comprehension is impaired as is speech, which soon becomes unintelligible or completely lost. Spastic paralysis develops progressively, eventually leading to quadriplegia with contractures in extension of the lower limbs and in flexion of the upper limbs.

In addition to these contractures, there are tonic fits which lead to opisthotonos and exaggerate the contractures. These tonic fits are precipitated by the least sensory stimulus. True epileptic seizures as well as choreo-athetotic movements may occasionally occur and nystagmus and oculomotor disturbances are frequently observed. Increased intracranial pressure may occur with accompanying papilledema, but this is transitory and the optic fundus is usually normal or shows varying degrees of optic atrophy.

Mental difficulties worsen progressively until complete dementia is reached coupled with blindness and deafness of cortical origin. Contractures become worse until the patient presents the picture of decerebrate rigidity. During this period there may occur wide variations of body temperature. Death is usually due to cachexia, bulbar difficulties or intercurrent infection.

To this description should be added the remark that a purely psychiatric picture may dominate the clinical picture especially in the adult cases.

Historical review

In 1885 Pelizaeus described clinically five cases of a hereditary disease of the central nervous system and in 1907–1908, Merzbacher, in tracing the history of a case of diffuse sclerosis in a brain which had been sent to him for examination, discovered that there were several more siblings similarly affected in a family related to Pelizaeus' original cases. Merzbacher published his findings in fourteen members of this family in 1910.

After the Haberfeld-Spieler-Schilder case, the next report was that of Krabbe in 1916, who described five cases distributed among three families. In his cases, as in the Pelizaeus-Merzbacher type, the disease started during the first months of life; but it ran a course of only a few months in Krabbe's cases while in the Pelizaeus-Merzbacher group the disease ran a very slow chronic course over a period of a few years.

In 1925 Scholz described familial cases affecting children, the disease running a subacute course, and in 1927 Ferraro added the adult, chronic type of a familial "diffuse sclerosis." Finally, in 1936, van Bogaert and Nyssen described a late adult type. A classification of this familial, degenerative type of "diffuse sclerosis" based on clinical characteristics mainly as described in these cases became widely accepted and consisted of five categories:

1. The acute, infantile type of Krabbe
2. The subacute juvenile type of Scholz
3. The adult type of Ferraro
4. The late adult type of van Bogaert and Nyssen
5. The chronic type of Pelizaeus-Merzbacher

Other types of leucodystrophies were described which were based on some particularities of the histopathological observations. In 1924, Collier and Greenfield reported unusual large epithelioid or globoid cells in a case of "diffuse sclerosis." In 1933, Greenfield described a form of progressive cerebral sclerosis in infants associated with primary degeneration of the interfascicular glia. Finally, in 1938, Einarson and Neel coined the term "leukoencephalopathia progressiva metachromatica diffusa" because of the presence of large amounts of metachromatic staining material in a case of diffuse sclerosis.

As more and more cases of leucodystrophy were published it became apparent that neither the age of onset nor the duration of the disease nor whether the disease was familial were sufficient criteria for classification. Possibly closer examination of the pathological characteristics of these different categories might yield a better basis for differentiation.

On reexamining the original publications it has become evident that there are other characteristics of a histopathological nature which make a different classification imperative. Recent histochemical and biochemical investigations are providing support for this newer classification.

To summarize, Collier and Greenfield laid stress on the presence of globoid cells as a special feature of those cases which had previously been described by Krabbe in his cases and which were again found by Ferraro in his adult type. When Brain and Greenfield described more cases of "diffuse sclerosis" associated with degeneration of the oligodendroglia, they found that the abnormal material gave a metachromatic staining reaction and were thus related to Einarson and Neel's cases as well as to several previously published cases of metachromatic leucodystrophy. Van Bogaert and Nyssen's case was identical in its characteristics to Scholz's subacute juvenile cases.

General histopathological picture

There are basic overall histopathological features that make it possible to separate the leucodystrophies from the other entities previously included in the eponymic designation of "Schilder's disease." The demyelinization is diffuse and it is almost always symmetrical; it habitually involves both cerebral and cerebellar hemispheres; the edges of the lesion are poorly demarcated except when the demyelinizing process reaches the U-fibers which are rarely destroyed. The cortex is seldom involved, and the myelin-axonal dissociation is frequently lacking, the axons being almost always involved in the same degree as the myelin sheaths; pyramidal tract degeneration is an almost constant feature. Perivascular reaction is very variable, although it is most frequently minimal or even absent. This is a manifestation of the speed of evolution of the disease process; i.e., the severity of myelin disintegration, the intensity of which determines the inflammatory reaction. There is diffuse isomorphic gliosis which may well show reinforcement around the ventricles, the blood vessels, and at the junction of white and gray matter.

Special criteria which form the basis for subdivision of leucodystrophies into several different types are: preservation of islands or strands of intact myelin in areas otherwise severely demyelinized, type and abundance or lack of glial reaction, presence of globoid cells, presence of intermediate products of myelin catabolism, presence of abnormal large naked glial nuclei, status spongiosus of gray and subcortical white matter.

For purposes of discussion, the leucodystrophies are here divided into the following categories:

1. Pelizaeus-Merzbacher disease
2. Leucodystrophies with “glial insufficiency”
3. Globoid-cell type
4. Spongy degeneration of the neuraxis

Pelizaeus-Merzbacher disease

The inclusion of Pelizaeus-Merzbacher disease in the group of leucodystrophies is not universally accepted. However, all cases that have been examined pathologically fit the criteria for leucodystrophies that were outlined above.

In Merzbacher’s 1910 paper he described the following clinico-pathological syndrome as characteristic of a familial type of “diffuse sclerosis”:

The disease starts rather early in infancy but progresses extremely slowly with a very chronic course. It is characterized by speech disturbances, bradylalia, foolish grimacing, ataxia, intention tremor, athetosis, choreiform movements, spasticity and mental deterioration. The histopathological features of the brain are an extensive diffuse symmetrical demyelinization and sclerosis of the white matter of the cerebrum and cerebellum with considerable involvement of the axis cylinders. The most remarkable finding is that scattered throughout the large areas of complete demyelinization there are small areas with intact nerve fibers and myelin sheaths. The U-fibers are spared throughout.

The essential points were thus the familial incidence of the disease and the presence of preserved islands of myelin. Merzbacher’s stress upon preservation of the U-fibers as a criterion soon was discarded as it became recognized that those fibers were very frequently spared in many different types of diffuse demyelinating diseases.

Study of other cases of this condition revealed two other important characteristics: that there was a rather striking paucity of macrophages and that the few which were present contained sudanophilic material. It then would appear that myelin catabolism proceeded normally to its neutral fat end stage.

Let us now examine the value of the other bases for differentiating this disease from other types of leucodystrophies.

1. The clinical picture is far from characteristic, since a similar one has been reported in many cases of bilocular or transitional sclerosis and leucodystrophies. The slow chronic course is also not a sufficient criterion in itself for the same reason.

2. The presence of preserved islands of myelin has also been reported in cases of bilocular or transitional sclerosis (Matthys, Kornyey, Poser) as well as in cases of globoid-cell leucodystrophy (Kaijser and Lundquist, De Lange [1950]). Lowenberg and Hill's case strongly resembled the picture described in the instances of CO intoxication by Schenk and by De Lehoczky. It was only later shown by Camp and Lowenberg that the case was familial. Althrough it is true that in the reported instances of Pelizaeus-Merzbacher disease there are many such islands, in some of them the islands eventually disappear to give way to a complete demyelinization including myelinated fibers in the gray matter (as in Seitelberger's cases), a picture that has been described in other leucodystrophies (van Bogaert and Scholz, Frank, Jacobi). The islands of preserved myelin are usually not perivascular as they are in Lowenberg and Hill's case.

3. With regard to the familial incidence of the disease, the best recent review of the subject was by Seitelberger in 1954. In addition to his own three cases, all in siblings, he accepted eight cases originally reported by other authors as familial ones and four cases as sporadic instances of Pelizaeus-Merzbacher disease. To those four must be added Blackwood and Cumings' case II. Even though Seitelberger included Sherman and Liebert's case, the information they presented is inadequate for exact classification.

4. The age of onset of those cases in some instances hardly corresponds to Pelizaeus-Merzbacher's original criteria: in Lowenberg and Hill's case the disease started at age 43, in Bielschowsky and Henneberg's at 9, in Einarson and Neel's case II at 10.

Seitelberger stated to support his belief that Pelizaeus-Merzbacher should be included in the leucodystrophies that

> "the peculiar demyelinization in Pelizaeus-Merzbacher's disease has to be considered a form of degeneration of the myelin sheath which is independent but endogenously conditioned and it therefore belongs among the leucodystrophies. The difference between Pelizaeus-Merzbacher and the other known types of leucodystrophies is the fact that there are absolutely no histomorphological changes in the structures

serving the metabolism of the myelin sheath. From this the conclusion could be drawn that there is an insufficiency of the glial apparatus, which has been accepted by many authors as the basic criterion for the diagnosis of leucodystrophy on histological grounds."

Only one case of Pelizaeus-Merzbacher disease has been examined to date by biochemical means and reported on. Blackwood and Cumings studied the brain of a fourteen-year-old girl with that disease (their case II) and found that there was a decrease of all brain lipids in both gray and white matter. Cholesterol esters were absent except for a small amount in the cortex. They interpreted these results as follows:

"The absence of cholesterol esters in the white matter suggests that active demyelinization is not occurring here and this, taken in conjunction with the general reduction of all lipids to a level found in the brain of a child of not more than two years of age, suggests that myelinization had proceeded normally to about this age, after which normal development had not taken place."[1]

In 1955 Seitelberger followed up his histological study of Pelizaeus-Merzbacher disease by a histochemical investigation of one of his three cases. Using a battery of staining and solubility tests he arrived at the following conclusions: in Pelizaeus-Merzbacher disease, even though the myelin sheath disappears as a morphological structure, there remains in its place a fatty sheath which contains the typical lipids (sphingomyelin and cerebrosides) of normal myelin. This corroborates Edgar's contention that the usual myelin sheath stains (Weigert, Heidenhain, Spielmeyer) do not always reveal the true state of that structure. Seitelberger felt that these staining methods do not color the lipid components of the sheath but rather the lipid-protein structural network. Thus he concluded that in Pelizaeus-Merzbacher disease a specific lipid fraction of the myelin sheath as well as its protein skeleton are lost, while the sphingolipids are preserved. This would also explain why few if any products of myelin disintegration are found.

From his histochemical results it would appear to be the glycerophosphatidic fraction that is lost. Because of that he proposed that while the other forms of leucodystrophies might better be called "sphingolipid dystrophies of the myelin sheath," Pelizaeus-Merzbacher disease should perhaps be considered a glycerophosphatidic dystrophy.

These theoretical speculations, however interesting they may be, need further corroboration before they can be accepted.

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[1] Edgar (personal communication) has since found a significant increase of hexosamine in the white matter of the brains of three cases of Pelizaeus-Merzbacher disease. This would tend to support our intention to place this disease among the leucodystrophies.

Cases of neutral fat leucodystrophy

Hallervorden (as cited by Diezel) had suggested the possible existence of cases of neutral fat leucodystrophy which would not be instances of Pelizaeus-Merzbacher disease. Actually Einarson, Neel and Strömgren's case XIV, Tans' case, and Jervis' case (which was combined with progressive muscular dystrophy) are of that type as are Edgar and van Miert's case as well as two yet unpublished cases of Peiffer. Einarson, Neel and Strömgren's case XII is worth noting in that the authors stated they had found large amounts of prelipoid as well as neutral fat material in approximately equal quantities in the white matter of the cerebral hemispheres. Weber also reported a case of leucodystrophy in which all the macrophages contained neutral fat except for a few small areas containing prelipoid material. Biochemical investigation of these cases may well reveal their nosological positions as well as their relationship to Pelizaeus-Merzbacher disease.

The neutral fat leucodystrophies might seem to represent familial instances of S.C.S.; however, these cases are classified as leucodystrophies not on the basis of histochemical staining properties of myelin Abbau but rather on the basis of their general histopathological characteristics.

Leucodystrophies with "glial insufficiency"

In 1925 Scholz described a case of familial "diffuse sclerosis" in a child and brought attention to the fact that the products of myelin catabolism, instead of taking a brilliant red color with the usual fat stains, became a dull rose or yellowish-red. He felt that this material belonged to the group known as prelipoid, and postulated that something was amiss with the glia in that their enzymatic action upon degenerating myelin had been impaired, possibly by some congenital defect or deficiency.

This theory was adopted by Bielschowsky and Henneberg in 1928 and many authors have subsequently subscribed to it. Later the "Scholz type" of leucodystrophy, which had previously been classified as such on the basis of the age of onset, became better defined on a histochemical basis. To classify on a purely histochemical basis, however, is a dangerous procedure.

Before considering myelin catabolism in the leucodystrophies, it might be worthwhile to review briefly the known facts about normal myelin catabolism. Einarson and Neel outlined in 1942 the following scale of decomposition products:

1. Anisotropic droplets
2. Anisotropic and metachromatic material
3. Purely metachromatic material
4. Simple basophilic material
5. Eosinophilic material which also stains blue with hematoxylin
6. Material staining pale reddish-yellow with scarlet dye, called prelipoid
7. Material staining brilliant red with the usual fat stains.

They went on to state that:

> "Of course all these stages cannot always be sharply distinguished from each other as the one proceeds gradually into the other and hence their separation must be somewhat diagrammatic. Certainly the stages 4, 5 and 6 are so intimately connected that they are hardly to be separated while the stages 1 and 2 appear to be coexistent in the Marchi stage."

De Vries says that the normal process of myelinization in fetal and post-natal life and the normal metabolism of the myelin sheaths are known to occur without the apparent transportation of lipoid substances by phagocytes or other cells. When the lipoid or prelipoid is combined with a protein substance, it becomes soluble in tissue fluids. Normal catabolism may take place without the help of the glia although it would seem that the oligodendroglia may furnish the enzymes necessary for this lipoid-protein bondage.

In many cases these diseases start in early infancy or childhood, at a time when myelinization is still in progress. This fact led Bielschowsky and Henneberg in 1928 to raise the possibility that the disturbance is not in myelin catabolism but rather in anabolism. It is still possible, however, to apply the concept of glial insufficiency in this situation if the role of the oligodendroglia in myelin anabolism is accepted. In support of this contention, Greenfield pointed out in 1933 that when there was primary degeneration of the oligodendroglia in his cases, the areas affected by the demyelinizing process were those most recently myelinated.

If abnormal myelinization can account for cases starting early in life, another explanation must be found for those in which the central nervous system and all its myelinated systems function adequately for many years and demyelinization occurs in adult life. Here, of course, the final answer must await the discovery of the primary myelinolytic mechanism.

The orderly evolution of degenerating myelin catabolism is governed by quantitative factors; i.e., the glia and macrophages can handle only certain amounts of the material. This means that if there is an overwhelming amount of degenerating myelin resulting from a very active phase of the disease, it is quite possible that some of the Abbau products will be found in intermediary stages of decomposition. Thus the presence of prelipoid material alone is not enough to establish the concept of glial insufficiency.

Einarson and Neel have attempted to solve the problem of pathogenesis of demyelinating diseases in general, not only of the leucodystrophies, in the following manner. They postulated the existence of four "tissue factors":

1. The extrinsic dystrophic tissue factor: a constitutional insufficiency of the interfascicular glia in dealing with the nutrition of the myelin sheath.
2. The extrinsic dyscatabolic tissue factor: an insufficiency of the microglia in dealing with the abnormal metabolic prelipoids and degeneration products of the myelin sheaths.
3. The extrinsic histochemical tissue factor: the biological action (stimulating or inhibiting) of the atypical metabolic degeneration products on the atrocytic apparatus.
4. The intrinsic dysplastic tissue factor: the inherent individual tendency of the macroglia toward proliferation and blastomatous growth.

They felt it is the interplay of these various "factors," of which the importance of each varies from case to case, that determines the final pathological picture.

This rather mechanistic approach to the problem implies that the "factors" affect the basic process, while it is the present authors' firm belief that the reverse takes place and that the four "factors" should really be considered stages or manifestations of the disease in the various tissue components.

The presence of abnormal products of myelin catabolism is by no means restricted to cases of leucodystrophy: Balo reported finding prelipoid material in a case of combined-system disease; Matthys found large amounts of this material in a case of transitional sclerosis, which he erroneously classified on that basis as a leucodystrophy; Einarson and Neel's case VII, which is an instance of diffuse glioblastomatosis, also contained prelipoid material as did Bielschowsky and Henneberg's third case which is classified as an instance of Pelizaeus-Merzbacher disease.

Furthermore, the abnormal material present in cases of leucodystrophy does not always give a yellowish-red prelipoid reaction with fat stains. If the so-called metachromatic reaction were not considered, there would be several cases which would seem difficult to classify depending solely upon histochemistry, although the general histopathological characteristics are undoubtedly those of leucodystrophies: such cases include Balo's (1940), De Lange's (1946), and Frank's

(1947). It is probable that in those cases the phagocytes are filled with mixtures of products of myelin catabolism at different stages of disintegration, perhaps each with different staining properties.

In 1933, Greenfield described a series of cases of leucodystrophy characterized by primary degeneration of the interfascicular oligodendroglia. At the time of the original publication no mention was made of the metachromatic staining reaction, but in 1950, in the second series of cases of that type, Brain and Greenfield mentioned the presence of large amounts of such material which was obviously derived from myelin breakdown. This was by no means the first report of metachromatic material in cases of "diffuse sclerosis." Alzheimer and Baroncini as well as Nissl had previously mentioned finding such material in cases of this type. Then came reports by Witte in 1921 and Kaltenbach in 1922. The latter, it should be noted, postulated some enzymatic deficiency of the scavenger cells. Following these there were many others.

It was, however, the oligodendroglial degeneration which was of importance since it fitted in so well with the prevailing theories of glial insufficiency that played a major role in the pathogenesis of leucodystrophies. Greenfield was careful to point out that oligodendroglia were absent not only from areas of demyelinization, a rather frequent occurrence in almost all types of demyelinization, but also in areas in which the myelin sheaths still seemed intact according to the usual staining methods.

Since then many authors have claimed the total or partial disappearance of oligodendroglia in their own cases. It should be pointed out, however, that not only do oligodendroglia almost always disappear from areas of demyelinization, but also that present staining techniques for oligodendroglia are far from satisfactory, so that it is often extremely difficult to judge the extent of loss of that particular type of glial cell. The metachromatic material found in those cases had another staining property which was important: that the material was mucicarmine positive. This also was consistent with the fact that oligodendroglia had been shown by Bailey and Schaltenbrand to undergo "mucinoid degeneration" in certain circumstances. Leslie, reviewing the published cases of metachromatic leucodystrophy, suggested a possible classification on the basis of whether the material was mucicarmine positive.

In his 1933 paper, Greenfield emphasized the fact that the abnormal material he saw in his case gave staining reactions similar to those of mucinoid material. Later it was shown by others that not all metachromatic substances were mucinoid in character. Since mucinoid substances frequently stain metachromatically, some cases in which they were found were erroneously classified as leucodystrophies. Thus the cases reported by Feigin as well as by Lowenberg and Cowie are perinatal encephalopathies with mucinoid degeneration. Mucinoid-metachromatic material has been found in a variety of conditions unrelated to the leucodystrophies: in Wilson's disease (Pelissier); in epidemic encephalitis (Lhermitte, Krauss and Bertillon); in senile brains (Grynfeltt; Claude, Lhermitte and Baruk); in transitional sclerosis (Coenen and Mir, Schaltenbrand); and in fat embolism (DeVries). It is interesting that in DeVries' leucodystrophy he found two types of material: one was mucin-negative and metachromatic, while the other failed to stain metachromatically but stained red with mucicarmine.

We still know too little about he influence of various fixatives and mounting agents upon the abnormal material contained in those cases to be able to claim fragile staining reactions as a basis for classification. Most of these cases are stained after formalin fixation, and since van Bogaert and De Wulf pointed out that lipochrome will stain metachromatically after such fixation, one might wonder at the significance of metachromasia in other lipid materials. The association between metachromasia of myelin catabolic products and primary oligodendroglial degeneration was weakened by the publication of Bertrand, Thieffry and Bargeton's case in which prelipoid nonmetachromatic, non-mucinoid material was found at the same time as a primary degeneration of interfascicular oligodendroglia.

The so-called metachromatic cases served the extremely useful purpose, none the less, of attracting attention to the relationship between the leucodystrophies and the lipoid storage diseases: Witte, in 1921, was the first to suggest this possibility when he found abnormal (and also metachromatic) material in the liver, kidney, pituitary, and testes of a case of leucodystrophy the brain of which contained the same material. Following this, Norman (1947), Brain and Greenfield (1950), Einarson (1954), and DeVries (1954) also reported the same finding in liver, kidney, or gall bladder.

This visceral involvement, however, is not restricted only to the metachromatic cases. Scheidegger reported finding prelipoid material in the spleen of his case and Bertrand, Thieffry and Bargeton found the same type of material in the liver and spleen of their case.

The origin of this visceral material has provoked some controversy, one school holding that it simply represented the reticulo-endothelial system's way of handling the "overflow" of this material from the brain while another maintains that it is the expression of a generalized metabolic disorder akin to the lipidoses. The latter theory has gained some support from the fact that abnormal Abbau material was found within swollen neurons in metachromatic cases (Nissl; Norman; Brain and Greenfield; Leslie) as well as in prelipoid cases (Wicke; Frank; Scheiddeger; Bertrand, Thieffry and Bargeton). Fruitful biochemical investigations arose from such similarities between leucodystrophies and lipidoses.

Perhaps the best way to consider the question of the metachromatic leucodystrophies is to remember first, that in normal myelin catabolism, the Abbau material passes through a metachromatic stage; second, that it is difficult to separate the different stages from each other since speed and intensity of catabolism may vary widely from case to case; and third, that metachromasia is an evanescent and nonspecific staining property which will give different results under different circumstances.

Greenfield was very much aware of the difficulties in setting up criteria for delineating this type of leucodystrophy. He went into elaborate detail in describing the conditions of fixation, mounting, and staining necessary to establish a case as truly metachromatic. He refused to accept Carillo's case as a metachromatic one because the abnormal material in the latter's case stained green with toluidine blue instead of red. Probably the same objection would have excluded Brandberg and Sjovall's case because there toluidine blue resulted in a yellow-orange stain. Norman and Leslie, however, considered the case as an instance of metachromatic leucodystrophy.

It has been the experience of many investigators that products of myelin catabolism may give metachromasia in frozen sections but not in paraffin sections even though the material has not been dissolved out, and that the solubility may vary considerably from case to case. In general, most authors agree that metachromatic material, when stained with Scharlach, gives a dull red or yellowish-red color that has become recognized as characteristic of prelipoid material, which is probably a complex mixture of lipids.

Of clinical interest is the fact that when Witte found metachromatic material in the renal tubule epithelium, he suggested that perhaps one could find casts of metachromatic material in the patient's urine. No such finding has yet been reported in the literature, but Austin was able to demonstrate exactly that in the urine of an autopsy-proven case of metachromatic leucodystrophy as well as in the urine of a brother with an identical clinical picture. Such examinations, coupled with liver chemistries and renal function studies, perhaps even liver biopsies, might give valuable clinical information in some cases of leucodystrophy.

There remain some cases which would seem to belong to the category of "glial insufficiency" leucodystrophies even though they present certain unusual features.

In 1943 Josephy and Lichtenstein reported two instances of diffuse leucoencephalopathy in two siblings. The autopsy report on one of them revealed that the entire white matter had been replaced by a semi-liquid mass and that there was a complete absence of any kind of glial response. This case represents the most complete type of glial insufficiency, and therefore of leucodystrophy according to the Bielschowsky-Henneberg definition.

The cases reported by Frowein and Krucke, by Lowenberg and Fulstow, and by Suckow and Lange-Cosack are still of a different type. In the first one, in addition to the presence of prelipoid material and neutral fat in the macrophages, there was so-called idiopathic calcification of some of the vessels and amyloid degeneration of others. In the second case there were huge amounts of hyaline material present which had replaced the myelin; while in the third, although few details are given, there was said to be cortical calcification reminiscent of what is found in Sturge-Weber syndrome. These cases are extremely important since they point to a possible relationship between the leucodystrophies and other metabolic disorders of calcium or protein.

In summary, it appears that differentiation of the "glial insufficiency" type of leucodystrophy into several subtypes such as the prelipoid or the metachromatic type, each with its own subdivisions, is of dubious value. It seems best simply to characterize it by the presence of intermediate products of myelin disintegration which may well be the result of some kind of glial insufficiency. Biochemical determinations so far have supported this conclusion.

Brante reported in 1952 that he had found an increased neuraminic acid content of the white matter in two cases of the metachromatic type of leucodystrophy. Cumings in 1955 studied two cases of metachromatic leucodystrophies and found that the phospholipid content was diminished and that there were no cholesterol esters, but that there was a marked increase in hexosamine content.

The most extensive investigation of such cases has been carried out by Edgar, who reported in 1954 and 1955. He found that:

1. The hexosamine content of brains with bilocular or transitional sclerosis of the Schilder type was within the same range as that for the brains of normal children of comparable age.
2. The brains of six cases of the metachromatic type and five cases of prelipoid type all had significant elevations of the hexosamine

content. On the basis of this determination, it was impossible to differentiate between the two types.

Peiffer and von Hirsch reported in 1955 using a histochemical method in which they employed an acetic acid solution of cresyl violet. They found that the abnormal material present in these cases of leucodystrophy gave a brownish metachromasia regardless of the fact that in some cases other stains had revealed the presence of prelipoid or metachromatic material. In addition, they found that this brownish material was present within nerve cells in certain areas such as the dentate nuclei, the inferior olive, the red nucleus, the vagus nucleus, the anterior horn cells, and the pallidum and thalamus. They concluded that this material was a glycolipid, probably a ganglioside, but that it was different from the ganglioside that Klenk had extracted from his cases of Tay-Sachs disease. The results obtained by Edgar on the one hand and Peiffer and von Hirsch on the other seem to be powerful supports to the contention that there is no essential difference between the prelipoid and the metachromatic types of leucodystrophy.

A word should be said about the staining reactions of the myelin disintegration material found in Schilder's 1913 case. The fact that the material in the macrophages stained pink with Nile Blue sulphate and was Ciaccio positive was interpreted by Lumsden as conclusive evidence for its prelipoid nature. The 1909 Ciaccio method, according to Pearse, stained positively (red) both saturated and unsaturated phospholipids (lecithin, kephalin and myelin) and mixtures of cholesterol and cholesterol esters. Kaufman and Lehman (cited by Pearse) conclude that all Ciaccio-positives were unsaturated fats and that the reaction was specific for those. Pearse also states that pink staining with Nile Blue sulphate indicates the presence of unsaturated fatty acids. It is interesting that in some of the metachromatic cases of Brain and Greenfield, part of the material indeed stains pink with Nile Blue sulphate. Edgar's belief that deep blue staining with Nile Blue sulphate is characteristic of prelipoid material may well need re-examination in view of what was found in case of leucodystrophy examined in this laboratory: Scharlach and Sudan stains revealed the presence of dirty yellowish-red material consistent with what is called prelipoid material, but this substance failed to stain with Nile Blue sulphate as well as with the McManus technique. We know too little about the nature and individual staining reactions of the different components of the mixture we call "prelipoid" to rely upon histochemical staining reactions alone.

The globoid cell type of leucodystrophy

In 1924 Collier and Greenfield brought attention to the presence of a special type of cell in cases of "diffuse sclerosis." Their description was as follows:

> "In all regions where myelin destruction was active, particularly in those regions where it appeared to be of more recent date, there were large globoid cells of peculiar character. Their nuclei were always multiple and sometimes were numerous and were arranged as a chain of thin flattened nuclei under the capsule of the cell. In size, these cells were remarkably uniform, the smallest being 30 μ and the largest being 50 μ. Their cytoplasm was almost clear or at most very finely granular and with Scharlach R only gave a diffuse pale brick color similar to that seen in the large fiber-forming glial cells. Those cells often lay in small groups or in small clusters collected around blood vessels. Their complete lack of processes was illustrated by the readiness with which they dropped out of frozen sections."

Such cells had been described previously, however, in cases of "diffuse sclerosis." Beneke was probably the first to do so, in 1908, although his case may not be a true leucodystrophy but rather a special type of transitional sclerosis since in addition to the area of "diffuse sclerosis" there were plaques of demyelinization elsewhere. Krabbe published his famous cases of acute infantile familial diffuse sclerosis in 1916, and although he gave a good description of the globoid cells he did not emphasize their significance. In 1922 Neuburger also described them, but again in a case that may well be a transitional sclerosis rather than a leucodystrophy.

The presence of globoid cells has now become recognized as a cardinal histopathological feature of a special type of leucodystrophy. Unfortunately, many different types of cells have been termed globoid cells although they do not really correspond to the original description of Krabbe or Collier and Greenfield. There is considerable doubt that the cells described as globoid by Guillain, Bertrand, and Gruner are true ones but are more probably morulated plasmatocytes.

Because Krabbe had stressed mainly the early onset and fairly acute course of the disease, which he called "infantile type of familial diffuse sclerosis" in his 1916 communication, it became a repository for a group of familial demyelinating diseases which had in common just those clinical features. Among this group were certain cases of globoid cell leucodystrophy corresponding to Krabbe's original description, but also instances of other types of leucodystrophies and a number of perinatal vascular or anoxic encephalopathies.

Even though it is true that most of the globoid cell leucodystrophies start early in life, three cases described by Ferraro in 1927 which became accepted as the adult type of familial "diffuse sclerosis" make a glaring exception. Ferraro himself, none the less, felt that the globoid cells found in his cases were identical with those described by Krabbe and by Collier and Greenfield.

The globoid cell cases, like the other leucodystrophies, have the same histopathological characteristics which were outlined previously but in these cases, in addition to the material contained in the globoid cells, the products of myelin Abbau that are found consist of sudanophilic neutral fat.

The nature and origin of the globoid cells has puzzled many investigators. In 1948 Hallervorden had suggested the possibility that the globoid cells were identical with the cells found in the spleen in Gaucher's disease. He also thought that they might contain kerasin, the cerebroside found in excess in Gaucher's disease.

Blackwood and Cumings studied a case of globoid cell leucodystrophy (their case III) in 1954 and found there were no cholesterol esters present, that there was considerable diminution of phospholipids, that the neuraminic acid and hexosamine content of the white matter were normal, but that there was a considerable increase in the cerebroside content of the white matter which they attributed to the material contained in the globoid cells. On the other hand Brante, whose chemical analysis is included in Kaijser and Lundquist's case report, concluded that there was a diminution of all cerebral lipids in the white matter.

In 1955 Diezel, using extensive histochemical methods, compared three cases of globoid cell leucodystrophy to a case of Gaucher's disease. He found that in both diseases the content of the cells was a protein-bound glycolipid cerebroside but that there were histochemical differences between the "stored" material in the two conditions. He also disagreed with Blackwood and Cumings' findings since he discovered a diminution of total white matter cerebrosides in the cases of globoid cell disease.

In the same year Peiffer and von Hirsch, using their own histochemical methods, stated that the globoid cell type of leucodystrophy differed completely from the other type. They even questioned the lipid nature of the globoid cell material and suggested, because of its powerful tetrazonium reaction, that it might contain many aminated aromatic acids.

The origin of the globoid cells is also still in doubt and many investigators have advanced different theories based on morphological considerations. Neubürger, Greenfield and Hallervorden believed that they were of mesodermal origin while others such as Ferraro felt that they were derived from astrocytes. Blackwood and Cumings published very convincing photographs showing that the globoid cells were formed by microglia engulfing masses of abnormal material but Peiffer has just as impressive evidence to show that they originate from both microglia and astrocytes, although mostly from the latter. Finally, Einarson (1955), who originally felt that the globoid cells were derived from astrocytes, more or less dedifferentiated in the direction of neuro-epithelial-like cells, giving rise to a considerable polymorphism with transitional forms between astrocytes and oligodendroglia, now thinks that at least some of the globoid cells, especially those clustered round the blood vessels, may possibly arise from adventitia cells.

Leucodystrophy associated with spongy degeneration of the neuraxis

In 1949, van Bogaert and Bertrand published a paper entitled "Upon a Case of Familial Idiocy with Spongy Degeneration of the Neuraxis." They described a disease beginning in the first few months of life with lack of psychomotor development, severe hypotonia with eventual extension rigidity of the upper limbs coupled with involuntary movements, tonic neck reflexes and decerebrate attitude with optic atrophy without macular or retinal changes.

Clinically this syndrome resembled Tay-Sachs' disease or Krabbe's infantile familial "diffuse sclerosis." The histopathological picture was characterized by two special features in addition to diffuse demyelinization and sclerosis:

1. The presence of a status spongiosus of the deeper layers of the cortex and the U-fibers unaccompanied by perivascular cuffing or macrophages. Van Bogaert and Bertrand noted that the appearance of the status spongiosus area was suggestive of "chronic brain edema."
2. The presence of large, naked glial nuclei distributed throughout gray and white matter and somewhat resembling the cells which are occasionally found in Wilson's disease or the Alzheimer type II cells.

Similar cases had been reported previously under other names, most of them being classified erroneously as instances of the Krabbe type of "diffuse sclerosis." The first one was probably Globus and Strauss' case IV in 1928 which was called "progressive degenerative subcortical encephalopathy." Canavan published another such case in 1931 under the name of "Schilder's encephalitis periaxialis diffusa" and in 1937 Eiselberg reported two more which were called "infantile familial diffuse sclerosis." Finally Jervis published two very interesting cases in 1942 which were almost certainly related to this type because, although they did not show the typical spongy degeneration, the large, naked

TABLE 1

Some Clinical Data on Leucodystrophies.

Classification		Pelizaeus-Merzbacher	Glial insuffic.	Globoid cell type	Spongy Degener.
Number of cases known to exist		15	59	31	12
Age of onset		Cases	Cases	Cases	Cases
Age groups	birth	5		2	
	0– 6 mos	3		9	7
	6–11 mos			4	3
	1– 5 yrs	4	19	6	
	6–10 yrs	2	13	2	1
	11–20 yrs		7	1	
	21–30 yrs		5	2	
	31–40 yrs		1		
	41–50 yrs	1	2		
Average age of onset		4.7 yrs	10.7 yrs	3.9 yrs	11.7 mos
Range of age of onset		birth 43 yrs	15 mos 46 yrs	birth 29 yrs	2 mos 7 yrs
Duration of disease		Cases	Cases	Cases	Cases
	0– 6 mos		4	4	5
	6–11 mos		5	11	2
	1– 5 yrs	4	25	7	4
	6–10 yrs	3	6	2	
	11–20 yrs	7	4	1	
	21–30 yrs	1	2		
Average duration		11.3 yrs	4.7 yrs	1.8 yrs	10.6 mos
Range of duration		15 mos 24 yrs	3 mos 22 yrs	3 mos 12 yrs	4 days 2½ yrs
Familial cases		10	25	20	5
Only child		1	6		3
Consanguinity			2		2
Sex ratio	Males	12	32	15	7
„ „	Females	3	19	10	5

Notes: In addition to the above cases there exist 5 cases of neutral fat leucodystrophy and 9 cases of leucodystrophy that could not be classified. Three of the former and 4 of the latter cases are familial.

Only autopsied cases were included in this compilation.

Familial incidence was accepted even though not proven by autopsy in most instances. In two instances, the siblings were healthy but first cousins were affected by the disease.

Data on age of onset, duration of disease and family history was not recorded in all case reports.

glial nuclei were beautifully illustrated. Meyer in 1950 and Blackwood and Cumings in 1954 published more cases, and the authors have seen the brain of one case belonging to DeVries. In Blackwood and Cumings' case I, a twenty-three-months-old child, there was a smaller total content of lipids than was normal for a child of that age; in fact, an amount comparable to the content of the fetal brain. Preliminary work by Edgar on a brain of this type indicates that here too there may be an increase in the hexosamine content.

In some of the other reported cases (Eiselberg, Jervis, Meyer) a few macrophages have been found which contained sudanophilic material. Myelin catabolism thus did proceed to its normal end point although the macrophage reaction is very scarce. Hallervorden was the first to suggest including these cases among the leucodystrophies as a special type "with features of chronic brain edema" (cited by Diezel).

Familial incidence

It seems worthwhile briefly to examine whether a case can be stated with exactitude to be familial or not. It is only too seldom that a familial incidence is proven by post-mortem examination of siblings. More frequently only one case is autopsied, and clinical examination of siblings with clinically similar diseases must suffice to establish the incidence. In some instances the autopsied case is an only child; in others, there are too few siblings to establish familial incidence or lack of it on a sound genetic basis.

There is no question but that better follow-up and better genealogical investigations would shed light on true familial incidence in the leucodystrophies. A good example of this is the fact that Walthard's case (republished by Pfister) with two healthy siblings, and thus a possible sporadic case, turned out to be a cousin of Scholz's original 1925 cases.

Histochemical and biochemical considerations

The study of cerebral lipids, and in particular of myelin lipids, is a fairly new one, and its application to cases of "diffuse sclerosis" dates back only a few years.

It was the histopathological similarities between certain leucodystrophies, particularly the metachromatic cases, that led certain investigators to apply to cases of "diffuse sclerosis" the methods introduced by Klenk and his collaborators for measuring neuraminic acid as an index of ganglioside cerebral content in amaurotic family idiocy.

The results of the biochemical determinations carried out so far on cases of "diffuse sclerosis" of various types are by no means conclusive.

They only serve to point out new and possibly fruitful avenues of investigation toward better understanding and classification of these disease processes. They may also offer another pre-mortem, as well as post-mortem, diagnostic method for use with biopsy material as was indicated by Cumings (1955), especially when such material does not lend itself to histological study.

Brante, in 1952, was probably the first author to report that he had found an increase in white matter neuraminic acid in two cases of metachromatic leucodystrophy. These important findings are especially significant when one considers that gangliosides, as indicated by neuraminic acid, are not constituents of normal myelin, and thus that their increase cannot be taken simply as an index to myelin disintegration. The relationship between the gangliosides and the muco-polysaccharides contained in glial cells of course provided fascinating avenues of investigation which will undoubtedly test the validity of the glial cell-myelin sheath equilibrium theories.

In 1953, Cumings, and in 1954, Blackwood and Cumings, have studied demyelinating diseases and some of the leucodystrophies by using some of the new techniques in addition to the classical methods of total lipid determinations.

The fact that the neuraminic acid determination was based upon a colorimetric method which was greatly interfered with by myelin lipids, since they too gave color reactions, led Edgar to utilize a method using hexosamine as an index for ganglioside content which promises to be more accurate and less tedious than the neuraminic acid determinations.

It is important to remember Cumings' important finding that one of the characteristics of demyelinization as it occurs in cases of S.C.S., the presence of cholesterol esters which are normally absent from white matter, needs further investigation and study.

The biochemical methods used until now are far from perfect, and there are still many unanswered questions since in some of the hexosamine determinations, for example, there is a marked difference if one uses lipid extraction methods or the whole dried white matter for analysis (Edgar, p.c.).

Relationship between the leucodystrophies and other diseases of the central nervous system

1. *With the lipidoses*

The histopathological similarity between the leucodystrophies and the cerebral lipidoses, especially the amaurotic family idiocy group, had been noted and commented upon by Wicke in 1939 and Norman in 1947. The presence of myelin Abbau products in liver, kidney, etc. reinforced this contention.

In 1934 Bertrand and van Bogaert had pointed out that widespread demyelinization or arrest of myelinization was a rather frequent finding in cases of Tay-Sachs or Niemann-Pick's disease. Einarson reported a case in 1951 of amaurotic family idiocy with diffuse demyelinization of the hemispheres, including the U-fibers, and with "primary" degeneration of the interfascicular and subcortical oligodendroglia. This finding was confirmed in other lipoid storage diseases such as Gaucher's disease, Hand-Schuller-Christian disease, and cholesterolinosis.

The histochemical and biochemical investigations which have been carried out so far have borne out this relationship and some authors are ready to include some of the leucodystrophies in the general group of lipoid storage diseases. It would seem that more work is indicated before such a relationship can be established beyond any doubt.

2. *With familial spastic paraplegia*

In 1925 Scholz noted the presence of cases of familial spastic paraplegia in the genealogy of his patients with leucodystrophy. In 1930 Curtius reported upon an extensive investigation of the family to which belonged the two cases of leucodystrophy reported by Bielschowsky and Henneberg in 1928, and found several cases of familial spastic paraplegia. It did indeed appear that there might be a genetic relationship between the two diseases.

The present authors have had the opportunity recently to examine the brain of a child with a prelipoid type of leucodystrophy belonging to a family in which several members show clinical evidence of familial spastic paraplegia. It is unfortunate that to date there have been no reports of autopsies of such cases of paraplegia in families of autopsy-proven cases of leucodystrophy. The report by Kastan of a family in which there were cases of Pelizaeus-Merzbacher disease, Strumpell's familial spastic paraplegia, and leucodystrophy would be of much greater value had any of these diagnoses been established by pathological examination.

3. *With the cerebellar atrophies*

Macroscopic cerebellar atrophy is frequently observed in cases of leucodystrophy since the cerebellar white matter often participates in the demyelinizing process. However, there are certain cases in which there is atrophy beyond that of the white matter, expressed by marked loss of granular and Purkinje cells, resembling what is seen in the congenital cerebellar ageneses. Tans has published preliminary studies on such a case and Edgar and van Miert's unpublished case studied in this laboratory reveals the same characteristics. It is of further interest that in both instances myelin catabolism goes all the way to neutral fats.

4. *With the phakomatoses*

Divry and van Bogaert have published a case of prelipoid leucodystrophy in a patient who had two siblings with the same clinical picture. Autopsy revealed a diffuse cortico-meningeal angiomatosis resulting in numerous small cortical necroses in addition to the leucodystrophy. The skin showed some hair and pigmentary abnormalities suggesting a phakomatosis.

5. *With progressive muscular dystrophy*

Jervis has just published an interesting case combining a progressive muscular dystrophy with a leucodystrophy characterized by myelin Abbau going to neutral fat. The case is especially noteworthy in that there are four other members of the family who exhibit clinical pictures suggesting the same combination of diseases. All of these members, including the patient, issued from consanguineous marriages.

SUBACUTE SCLEROSING LEUCOENCEPHALITIS

In 1939, van Bogaert and De Busscher reported the case of a seven-year-old boy who presented signs and symptoms suggesting a brain tumor but having as characteristic features a rather marked agraphia and psychiatric difficulties. The disease evolved in a subacute fashion and the child died five months after the onset. At autopsy, it was noted that the entire white matter of the brain was involved by an inflammatory process which also affected the gray matter and was accompanied by a violent gliofibrillary reaction. In 1945 van Bogaert reviewed five such cases from the clinical and pathological standpoints and called the disease *subacute sclerosing leucoencephalitis.*

Clinical picture

The clinical picture presented by those cases as well as by cases seen since that time and reported in several publications is such that the clinical diagnosis can be made from its characteristic features.

1. The disease involves children.

2. It is progressive and subacute, ending in death after a few months.
3. There is early intellectual deterioration with rapid and severe involvement of all psychic function. Usually there is some element of agnosia, apraxia, and aphasia leading to complete dementia. Agraphia and diminution of scholastic ability are common.
4. There are convulsive episodes associated with complex dyskinesias and hyperkinesias of various types: clonic discharges, pseudo-choreic movements, ballism, myoclonic jerks, tonic fits with opisthotonus, or dystonic manifestations.
5. The course of the disease leads to decerebrate rigidity.
6. There are inconstant pyramidal tract signs.
7. The evolution leads to cachexia.
8. There are no constant or remarkable changes in temperature, pulse, etc., although febrile periods are not infrequent. Blood, urine, and spinal fluid examinations are within normal limits except that the spinal fluid Lange curve is often of the paralytic type.

In general, the disease progresses without remissions, and its progress may be divided into three stages according to the predominant symptom complex at the time: psychic and intellectual deterioration coming first, then various dyskinesias, finally rigidity and dementia.

Pathological picture

The pathological picture is almost as characteristic as is the clinical evolution of the disease. It consists essentially of subacute inflammatory reaction, made up largely of lymphocytes and especially of plasma cells, which extends diffusely throughout the axial white matter but spills over rather considerably at times into the cortex, the basal ganglia, and the thalamus. The myelin sheaths may be moderately or only minimally involved, while the fibrillary reaction is very active throughout the entire white matter. The lesions diminish on descending the brain stem, but may well be found in the spinal cord and even in the spinal ganglia. In certain cases cortical neurons have been observed to contain intranuclear or intracytoplasmic inclusion bodies.

In general the pathological picture reveals a diffuse type of demyelinization, somewhat motheaten in appearance, although the demyelinization may be completely absent. The gliosis is isomorphic; the axons may or may not be involved, depending on the severity of the process; the catabolism of myelin is carried out actively by the macroglia to the stage of neutral fats.

In this disease, as opposed to the other two prototypes under discussion, the electroencephalographic changes are pathognomonic for the condition. These observations were originally made by J. Radermecker in 1949 and they have been confirmed in all the cases seen so far and anatomically verified. They were also found by Cobb and Hill in some of the cases described by Brain, Greenfield, and Russell as "subacute inclusion body encephalitis of Dawson."

It is noteworthy that in 1944 Balthasar had reported on a series of nine cases of nodular panencephalitis of Pette-Döring. In his paper he gave EEG findings but did not emphasize the characteristics that were present in those tracings. These were later shown by Radermecker to be pathognomonic for subacute sclerosing leucoencephalitis and closely related diseases.

Summary of EEG findings (Dr. J. Radermecker)

The complexes are superimposed upon a basic rhythm which, as the disease progresses, becomes slower and more disorganized. The characteristics of the complexes are as follows:

1. They start with slow spike discharges, few in number, occasionally consisting only of a sudden deviation in the tracing or a brief notch on the ascending limb of the first slow wave.
2. High-voltage slow discharges, sometimes having the appearance of a deformed "K" complex, sometimes consisting of a train of slow waves of decreasing intensity and width, the whole complex lasting one or two seconds.
3. The fairly regular rhythm of those complexes, at least during the same tracing, with mean frequency of six to eight per minute, appearing diffusely in all leads but with a definite fronto-central predominance.

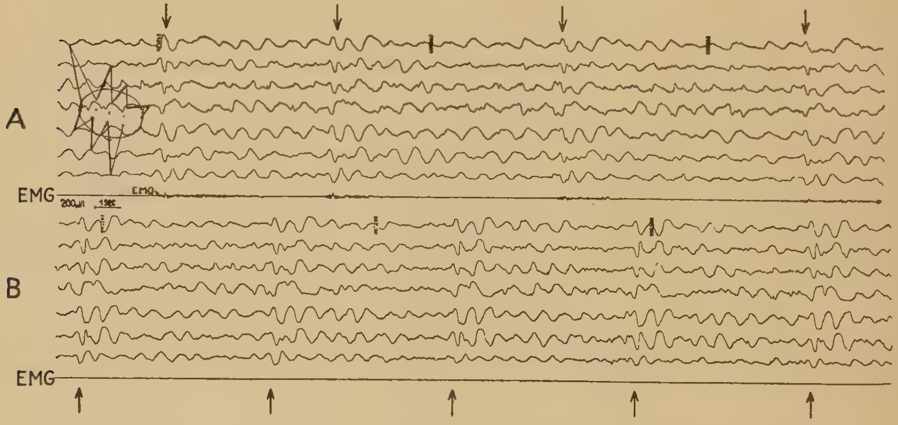

Fig. 2.

Electroencephalographic tracings from a case of subacute sclerosing leucoencephalitis.

A: waking record. B: sleep record. EMG: left biceps. Note that paroxysmal complexes continue during sleep while EMG records no myoclonic activity. The arrows indicate the characteristic complexes.

(From Martin, Macken and Hess, 1950. Courtesy Dr. R. Hess, Zurich).

4. The form of each complex remains the same in the same lead during the same tracing.

Following the complexes, the basic tracing may flatten out for one or several seconds before returning to the basic rhythm and the next complex. It is important to emphasize that the tracings and the forms of the complexes may vary considerably from day to day and may even be completely absent from some tracings for several days.

Early tracings frequently show the presence of bilateral synchronous spike, spike-wave, or even multiple-spike foci in the frontal or prefrontal regions which disappear with the progressive basic disorganization of the tracing.

The complexes are frequently synchronous with the myoclonic discharges as recorded in the EMG but not dependent upon them since the EEG complexes continue during sleep when the EMG is entirely normal.

Nosological situation

Cerebral biopsies have been added to the diagnostic armamentarium in subacute sclerosing encephalitis. Landau and Gitt reported having confirmed a case of the disease by this method, although the EEG and histological evidence is far from convincing, while Blackwood in 1955 biopsied six cases of subacute sclerosing leucoencephalitis and was able to make a diagnosis in only one. He points out that since the biopsies are most often taken from the frontal region, which is frequently not involved, the diagnosis may be missed.

Among the group of subacute encephalitides to which Schilder's 1924 case belonged, van Bogaert and De Busscher, in reporting a new case, delineated a particular type in 1939 and called it subacute sclerosing leucoencephalitis. Other groups of ill-defined atypical encephalitides had appeared in Europe after the disappearance of the great epidemics of encephalitis of the late 1910's and early 1920's. The case of Bodechtel and Guttman, reported in 1931, seemed to be the closest in type to subacute sclerosing leucoencephalitis. From their clinical and pathological descriptions, Bouman's case VI, Häsenjager and Lenz's case, Einarson and Neel's case X, and Rosanoff's case all may very well have been early reported cases of the same disease.

Pette and Doring in 1939 described a case which they called "panencephalitis" the pathological picture of which was strongly reminiscent of that seen in Japanese B encephalitis. The clinical characteristics were very similar to those of subacute sclerosing leucoencephalitis, but the histological details, coupled with the fact that there was relative sparing of the white matter, would seem to indicate that it is a different entity.

In 1948 Brain, Greenfield and Russell, and in 1950 Malamud, Haymaker and Pinkerton, described a series of cases of rather varied clinical as well as pathological characteristics in which the main pathological feature was the presence of intranuclear and intracytoplasmic inclusions of the type previously described by Dawson in a case of atypical encephalitis. Certain of those cases bear a great similarity both clinically and pathologically to the cases of subacute sclerosing leucoencephalitis described by van Bogaert and his collaborators. It is of more than passing interest that similar inclusion bodies have now been found in several cases of subacute sclerosing leucoencephalitis (Dubois, van Bogaert and Lhermitte; Martin, Macken and Hess; Geinert and Müller). A review of the relationship between van Bogaert's subacute sclerosing encephalitis and inclusion body encephalitis was published by Foley and Williams in 1953.

The nosological situation of subacute sclerosing leucoencephalitis in regard to the other types of subacute encephalitides has been thoroughly explored in Macken and Lhermitte's review in 1950, but it is far from having been resolved. The disease has undeniable histological similarities to general paresis, both clinically and pathologically it greatly resembles cerebral trypanosomiasis (Gallais and Badier, Janssen and van Bogaert). It is interesting to speculate upon the fact that all the atypical encephalitides, among which might be classified subacute sclerosing leucoencephalitis as well as Dawson's inclusion body encephalitis and Pette and Doring's panencephalitis or nodular encephalitis, were reported after the great epidemic encephalitides had disappeared. However, although the clinical and pathological characteristics of all three of these, as well as of many other examples of what are called "encephalitis," strongly suggest a viral etiology, no such agent has been discovered. As Lhermitte has suggested, it is possible, although it would be difficult to prove, that because of its subacute course and of the cerebral terrain in which it is found, subacute sclerosing leucoencephalitis represents a peculiar form of an already known type of encephalitis.

SUMMARY AND CONCLUSIONS

The authors have reviewed the different entities characterized by diffuse demyelinization and sclerosis of the cerebral hemispheres and which are commonly placed in the category known as Schilder's disease.

After an exhaustive survey of the available evidence they arrived at the conclusion that three main groups of diseases can be differentiated on a pathological basis.

The first one consists of what they have chosen to call *Schilder's cerebral sclerosis,* a disease closely akin to if not identical with disseminated sclerosis and which includes such variants as bilocular and transitional sclerosis, Balo's and Devic's disease.

The second group consists of the *leucodystrophies* which form a type of heredo-degenerative disease possibly related to metabolic disorders such as the lipidoses. This group may be subdivided into the following types: the Pelizaeus-Merzbacher, the glial insufficiency, the globoid cell, the type characterized by spongy degeneration of the neuraxis and a new, still not well known group of leucodystrophies characterized by the presence of neutral fats.

Finally, the *subacute encephalitides* make up the third group. Among those, van Bogaert's subacute sclerosing leucoencephalitis, Dawson's inclusion body encephalitis and Pette-Döring panencephalitis represent three sub-types which are closely related to each other.

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FROM THE RED CROSS HOSPITAL, OSLO

LESIONS OF THE CERVICAL SPINAL ROOTS AS A POSSIBLE SOURCE OF PAIN SIMULATING SCIATICA

By

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Around 1930 it became commonly realized that alterations of the lumbar spinal column might be the cause of sciatica. About ten years later it was realized that similar alterations in the cervical region might be the cause of brachial pain.

Previously a great number of causes had been named as the possible origin of "brachial neuritis", but even recent neurological text-books contain no mention of cervical columnar changes as the background of brachial neuritis (*Walshe* 1941).

Hyperostotic proliferations consequent to deformative spondylosis have been pointed out more than a hundred years ago (*Wentzel* 1824), and radicular involvement due to cervical spondylosis was reported in 1875 (*Braun*), although the view was favoured that secondary vascular changes and not direct pressure on the nerve was the explanation of the pain.

The cause of brachialgia has been the subject of much discussion and numerous publications on the subject have appeared, but few of them maintain the view that the pain is caused by direct pressure on the sensory fibres by osteophytes (*Bisgaard* 1932, *Lange* 1936). More attention has been pain to the important role played by protrusion into the spinal canal of the cervical discs, causing direct pressure on the spinal cord. It has been pointed out that this condition may resemble a number of neurological diseases, e.g. multiple sclerosis (*Russell, Brain et al.* 1952, *Russell, Brain* 1954).

Russell, Brain et al. emphasize that bosses and bars protruding into the spinal canal may compress the cord, thus giving rise to paresis of

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the lower extremities and to abnormal reflexes. They also stress the fact that the pressure on the cord may be intermittent, depending upon the position of the head and may be especially intensified by hyperextention of the neck.

Regarding the brachialgic pain, further important observations have been reported by *Frykholm* (1951). He has published a series of cases giving evidence that changes of the cervical discs are not necessary for the brachialgia to arise. He has pointed out that dural fibrotic alterations may provoke traction, angulation, and compression of the sensory fibres, and concluded that in such cases the logical treatment of the brachialgia consists in decompression of the nerve fibres under pressure.

In most cases of brachialgia obvious changes of the cervical spinal column are seen in the x-ray pictures, but similar visible changes may also be found to a strikingly pronounced degree without any brachialgic symptoms. The patient suffering from brachialgia may be completely incapacitated for any kind of work by a most excruciating pain. I have recently had referred to me a dozen of such cases on whom any attempt of treatment had been unsuccessful. In view of the failure of x-ray therapy, massage, short waves, traction, and medical treatment. I have treated some of these cases with decompression of the cervical spinal roots, in most cases with a dramatically beneficial effect. The operative procedure has been limited to a decompression of the spinal nerve within the intervertebral canal. A couple of cases from this series have been selected for publication, partly to illustrate the effect of this procedure on the pain, and partly because an analysis of these selected cases give evidence that myelopathy may arise even if the pathological changes of the cervical spinal column are limited to the intervertebral canal, causing no changes of the vertebrae or the discs of such a nature that the spinal cord is affected by direct pressure.

S.M., born July 25th 1909.—1931/54.

The patient was a male, referred to me by Dr. T. Asdahl because of pains and numbness along the ulnar side of the left hand and arm. On attempts to work the hand would get swollen and lose its strength. The pain was continuous and so strong that he could not sleep without antialgetic drugs.

He also complained of loss of control of the left leg, stating that he could not perform the movements of the limb as precisely as before, and the leg had lost some strength. At times he experienced a diffuse pain in the leg.

A few weeks before consulting me, he had been discharged from a neurosurgical service, where his condition had been investigated without finding indications for surgical interference. The discharge note stated:

"On admission were found a lesion of the left ulnar nerve with atrophy, loss of strength, and typical sensory changes. Inversion of the plantar reflex on the right side and hypesthesia of the dorsum of that foot, corresponding to the 5th lumbar root, were also observed. (In 1951 he had sciatica on the right side, also corresponding to a lesion of the 5th lumbar root). EMG indicated a peripheral lesion of the nerves to the arm. Myelography showed no abnormal findings. X-ray examination showed a lesion of the cervical intervertebral disc between C6 and C7 and spondylosis.

It has not been possible to point out a direct cause of the ulnar lesion of the patient. The curious inversion of the right plantar reflex was the reason for the myelography, which was negative. No indication for neurosurgical therapy has been found, and the patient was consequently discharged on the 12th of July, 1954."

When examined by me on September 1st, 1954, he presented the following findings: There were signs of an ulnar lesion, as mentioned above. The deep reflexes of the left leg were brisker than those of the right, and there was inversion of the plantar reflex on the left, and occasionally also on the right side. The abdominal reflexes on the right side were diminished. Otherwise the findings were as stated in the discharge note above, with the exception that the cerebrospinal fluid contained slightly increased values of protein (traces at a dilution of 1/20). The blood picture showed S.R. 27 mm; otherwise normal.

On September 30th, 1954, I carried out a cervical hemilaminectomy on the left side, decompressing the spinal roots within the intervertebral canals from C4 to D1. The abnormal findings consisted in a narrowing of the canal between C6 and C7 with scattered osteophytes projecting into the lumen of the canal.

The postoperative course was uneventful. He was out of bed after one week, and after two weeks he noted a definite increase in strength of the left arm with improved sensation in the regional distribution of the left ulnar nerve. On the sixteenth day he stated spontaneously that he could better control the movements of the left leg when walking. Examination showed that the plantar reflex had become normal and the deep reflexes of the legs were symmetrical and less brisk than before. The pain had disappeared from the arm and the leg.

COMMENT

There was no known cause of the illness. Apart from the signs of a cervical nerve-root lesion he gradually experienced pain in the left leg accompanied by a feeling of stiffness and lack of precision of the movements of the left leg. He stated that it felt as if the muscles and tendons of that leg were too short.

There were reflex changes in the left leg typical of a pyramidal lesion, with characteristic decrease of the abdominal reflexes on the same side to go with it.

The patient described the pain in the leg in such a way that it was reasonable to suspect a L 5 root lesion.

At the operation the intervertebral canal between C 6 and C 7 was first of all explored. The canal was slightly narrowed and contained a moderate formation of osteophytes. Although the canal seemed to offer space enough for the nerve, the space was limited, and it was conceivable that on certain movements of the neck the nerve might be pressed against the osteophytes.

Being somewhat dissatisfied with this finding as the only explanation of all the symptoms, I extended the operation to a hemilaminectomy from C 4 to D 1, exploring separately each root without being able to point out any other abnormal finding. It should be especially stressed that there was no intraspinal herniation of the intervertebral discs and there were no root sleeve fibrosis (*Frykholm*).

Since the operation the patient has up to date been relieved of his brachialgia, sciatica, unsteadines of gait, and the abnormal pyramidal signs. The cure by the decompression of the cervical root indicates that even apparently moderate changes limited to one intervertebral canal —without direct contact with the spinal cord —may give rise to a complex syndrome of which brachialgia, ataxia, abnormal pyramidal signs, and pain simulating sciatica are prominent features.

Below will be related the history of a similar case:

Aa.G., born March 4th, 1912.—2166/54.

The patient was a previously healthy woman referred to me by Dr. J. Valsö. Since 1946 she had suffered from pain in the left arm. During an attack of an acute febrile illness about Christmas time 1948 she experienced a most intense attack of pain shooting out to the left shoulder and arm and also in the left leg. She states that the arm became involuntarily flexed in the elbow joint and the leg was in a similar way pulled up by flexion in the knee and hip joint. The attack gradually subsided after a couple of hours, but considerable pain persisted for several days.

In the course of time the pain in the left shoulder and arm gradually increased and became a constant suffering during the last three years. The left side of the body had become hypersensitive to heat and she used to spend the nights in a sitting posture because that reduced the pain to a slight extent. When lying down in a horizontal posture, the left arm and leg were inclined to become "restless"—she then felt like fibrillations and small twitchings, at times as if an electric current was running through the limbs. Such episodes usually started with twitching in the arm, then in the leg on the left side, with increasing pains in both limbs.

On examination October 27th, 1954, when I first saw the patient she presented the findings as follows: There was atrophy of the muscles of the left hand and antebrachium, equally on the ulnar and radial side, more so of the hand than of the arm, with reduced strength of the movements. The deep reflexes of the left arm were sluggish as compared with those of the right arm, and the deep reflexes of the left leg were definitely brisker than those of the right leg.

The X-ray pictures of the cervical spine showed reduction of the discs between C4–C5 and C5–C6 with some lipping of the intervertebral joints.

On October 29th, 1954, I performed an operation consisting in a decompression of the cervical roots on the left side. The intervertebral canal between C4 and C5 was slightly narrowed and there were moderate but definite formations of osteophytes visibly projecting into the lumen of the canal. As these findings were limited and moderate as compared with the gravity of the symptoms, the exploration was extended to comprise all the intervertebral canals from C4 to D1, with otherwise normal findings.

Following the operation she passed a period of great pain in the arm and neck which gradually subsided in the course of a couple of weeks. The recuperation was delayed by a pulmonary embolus. A couple of months later she was entirely free of the old pain in the left arm and leg and showed normal and symmetrical deep and superficial reflexes in the legs.

She later developed similar pain in the right shoulder and arm, which became so severe that she decided to have a similar operation performed also on that side. She was again admitted to the hospital and on March 8th, 1955, I decompressed the cervical roots C4–D1 on the right side. The postoperative course was smooth, she was out of bed after 8 days and discharged after 3 weeks. Since then she has been free of the old pain, but occasional involuntary jerks of both lower limbs persisted for some time. After she had changed the position of her arms while at work these symptoms later entirely disappeared.

COMMENT

In this case also, the deep reflexes of the painful arm were decreased, while the deep reflexes of the homolateral leg were increased, as seen in cases of a pyramidal tract lesion.

Her pain in the shoulder and arm were excruciating. She had been under supervision of a series of doctors, had had massage, x-ray radiation, histamine, short waves and various sorts of “injections”. She had tried general medical treatment and psychotherapy and had finally been advised to marry, as the condition was considered to be psychic in origin, but this therapy she refused.

The primary aim of the operation was a decompression of the nerve roots inside the intervertebral canal C 5–C 6, where the x-ray picture showed osteoarthritic changes. This canal and also the one above were narrowed and were the seat of osteophytic proliferations. Any intraspinal alteration which might affect the cord was specially looked for, such as herniation or protrusion of the intervertebral discs or some other kind of encroachment on the cord or on the spinal nerve fibres. No such changes were present, and there was no root sleeve fibrosis.

The second operation disclosed on the right side findings of a similar nature and location as had been observed on the left side. Also on the right side the cervical roots from C 4 to D 1 were explored and decompressed. The procedure offered ample opportunity to examine both the medulla and the interior wall of the spinal canal in the cervical region, but no other abnormalities were observed.

DISCUSSION

Above, accounts have been given of two cases of brachialgia associated with pains in the lower extremity resembling sciatica. The neurological examination disclosed signs of a peripheral nerve lesion of the arm while the leg presented neurological changes indicative of a pyramidal tract lesion. The pathological anatomical changes were studied at operation and the condition proved to have an unusual background.

The primary aim of the operation was to carry out a decompression of the cervical nerves to which the pain was referred. In performing this procedure it was possible simultaneously to investigate the cavity of the spinal canal and the surface of the spinal cord and to look for any possible changes directly afecting the medulla. No such changes were present.

After decompression of the cervical nerve roots within the intervertebral canal the patient was relieved not only of the brachialgia, but also of the pain in the leg. Preoperative signs of a pyramidal tract lesion disappeared after the operation.

This clinical material is admittedly rather limited for definite conclusions. Although limited in number it possesses the advantage of having been scrutinized before, during and after the operation for the special purpose of elucidating the possible connection between the lesion giving rise to the brachialgia and the occurrence of the pain in the leg resembling sciatica.

The number of reports dealing with changes in the cervical spinal column as cause of brachialgia is rather limited, and they are of recent date. In the previously published material there have been demonstrable changes of the cervical discs with bony structure causing direct pressure in the spinal cord. It is now well-known that changes of such nature may be responsible for a lesion of the pyramidal tract (*Pallis et al.* 1952, *Russell, Brain et al.* 1952, *Russell, Brain* 1954).

The material presented here is distinguished by the fact that no such changes were present to account for the cord lesion. In the clientele described the pathological changes were restricted to the intervertebral canal, with no bosses or bars projecting into the lumen of the spinal canal. For this reason the cases presented here are not directly comparable to the clinical material referred to above.

Of a different nature is the series of cases published by *Frykholm* (1951). His material consists of cases where either no abnormality of the intervertebral disc was found, or, if present, it was of a lateral location causing no pressure on the cord itself, but exercised pressure only on the nerve root as it enters the intervertebral canal. An analysis of the cases operated upon by *Frykholm* yields interesting information in connection with the discussion of the cases accounted for here.

First of all it stands out that the coincidence of brachialgia and sciatica in his clientele is strikingly high. This fact has not, however, been specially pointed out by *Frykholm* and deserves some remarks in connection with the present discussion.

In no less than 20 per cent of the cases published by *Frykholm* the patient suffered from sciatica besides the brachialgia. It should be noted that according to the description of the operative findings by *Frykholm*, a lateral herniation of the cervical disc was found in two of the six cases complaining both of brachialgia and sciatica, while in the other four cases a root sleeve fibrosis alone was the only abnormal finding. The similarity between his cases and my material is therefore obvious in as much as the pathological changes affected the nerve root only and made no direct pressure on the cord.

In *Frykholm*'s material four of the six cases with the combined symptoms of brachialgia and sciatica, had the pain in the arm and the leg on the same side. In one case the report does not state in which leg the pain had its seat, and in one case the pain was located to the contra-lateral leg. In one of my cases the initial pain was in the contra-lateral leg, but later he developed pain also in the homolateral leg. In the other case reported here the pain was in the homolateral leg throughout the whole course of the illness. A homolateral preponderance thus seems to be the rule.

Frykholm states that one of his cases was submitted to operation because of sciatica. It is reported that the roots L 5 and S 1 were explored with negative result. This operation took place 18 days after the operation for the brachialgia, i.e. before it was possible to evaluate the possible effect on the sciatica of the cervical operation. Dr. *Frykholm* has kindly informed me that this patient has been under observation ever since the operation. While there has been some discomfort in connexion with the hands, the pain in the leg has never returned since the operation.

In an other of the cases reported by *Frykholm* showing both brachialgia and sciatica, the follow-up note yields information of interest: The patient (Case 27) suffered from brachialgia and sciatica, both on the right side. On operation it was found that the brachialgia was due to a root sleeve fibrosis. There was no protrusion of the disc. She passed a postoperative course of increased pain after which she improved satisfactorily and became free of pain in both extremities. However, eighteen months later she was operated on for a mastoiditis and experienced a *simultaneous recurrence of the sciatica and the brachialgia.*

In the four other cases of *Frykholm* showing both brachialgia and sciatica the follow-up note does not give any information regarding the sciatica.

So far it is difficult to offer an undisputable explanation of the *syndrome of "Brachialgic Sciatica"*.

The pain and its distribution which may occur in the legs of a patient suffering from an abnormality of the cervical spinal column may completely resemble a true sciatica. As pointed out in this discussion, even experienced neurosurgeons have mistaken the "brachialgic sciatica" for a lesion affecting the lumbar spinal root. In other cases the pain in the leg may be less typical of a true sciatica and prevail in the region of the knee or concern the whole lower extremity and clearly exceed the borders of one or two dermatomes. There is consequently only a doubtful justification for naming the pain a sciatica in the ordinary sense of the word.

The literature contains a considerable number of reports on cases of cervical interspinal disc protrusion with pains in the legs. This was e.g. so in the case reported by *Bedford, Bosanquet & Ritchie Russell* (1952), and in the cases reported by *Russell, Brain et al.* (1952). *Frykholm* has also given this problem much thought and believes that the simultaneous occurrence of brachialgia and sciatica in many cases is due to the fact that a patient who is susceptible to degenerative changes of the discs, may well have both a cervical and a lumbar localisation of this pathological alteration (personal communication).

In my opinion this and other proposed explanations are not satisfactory, as various circumstances seem to indicate:

First of all, it is improbable that a decompression of the cervical spinal roots may cure a sciatica actually caused by a herniation of a lumbar disc. In both my cases and also in the case reported by *Frykholm* (his Case No. 27) cure of the sciatica was obtained by a decompression of the cervical spinal roots to which the brachial pain was referred.

Next, it should be pointed out that a number of cases suffering simultaneously from brachialgia and sciatica have been explored at operation or at autopsy and it has been proved that no herniation of a lumbar disc was present. This, e.g., was so in the case reported by *Frykholm* on which a lumbar exploration was carried out with negative finding (his Case No. 1). It should also be kept in mind that in my case S.M. a myelography was performed because of a pain which was considered a typical sciatica, but there was no pathological finding.

Concerning the case reported by *Bedford, Bosanquet & Ritchie,* *Russell* (1952) a full post-mortem examination took place, but no herniation of a lumbar disc is mentioned among the findings.

The publications by *Russell, Brain et al.* (1952), *Bedford et al.* (1952), and several others have clearly shown that in cases of a cervical disc lesion with compression of the cord, the pains in the legs may be the initial symptom appearing even many years before the nucal or the brachial pain is registered by the patient. Any neurosurgeon of experience has explored case of sciatica supposed to be due to a lumbar disc lesion with a negative result, and it might be worth while to investigate if some such cases have proved to develop brachialgia at a later stage.

It has also been pointed out by the above authors that in cases of protrusion of a cervical disc with direct pressure on the cord, spasticity of the legs and reflex changes typical of a pyramidal lesion may be typical findings. My cases are distinguished by the fact that although no such direct pressure on the cord has been present, similar signs of a pyramidal tract lesion have been recorded.

After *Barré* had published his observations on “Le syndrome sympathique cervical posterieure” (1926) explaining the migrainous symptoms which may be associated with brachialgia as a result of compression of sympathetic fibres, this condition received considerable attention mainly by French neurologists, while others have explained it is “referred pain” (*Lewis* 1942).

In my opinion the syndrome is better understood by *Krogdahl & Torgersen* (1940) and by *Kovacs* (1955), who point out that deformities of the apophyseal joints with osteophytic proliferations may cause the symptoms by compression of the vertebral arteries. It is clearly illustrated by *Krogdahl & Torgersen* that exostoses may compress the artery nearly to complete occlusion.

It has been noted that in some cases the brachial pain may be provoked by certain movements of the head and neck because the movements may cause traction on the nerve roots beyond the point of tolerance.

In cases where spikes and bars or a periradicular fibrosis constrict the intervertebral canal, the space at disposal for the nerve roots within the canal may become insufficient, the nerve roots may become displaced and less mobile than normally, and such partial or relative fixation of the spinal nerve roots may cause secondary traction on the spinal cord. In cases of spondylosis of the cervical spinal column it has been observed by *Allen* (1952) during operation that the cord may blanch when the neck is flexed.

Normally there should be a considerable mobility of the dura within the spinal canal, and a still greater mobility of the cord inside the dural canal. Examinations carried out post mortem by *Frykholm* (1951) has shown that even normal ventroflexion of the head and neck resulted in a slight but distinct upward movement of the dural sack. The movement was more noticeable in the dorsal part of the sack than in the lateral part. The upward movement of the root pouches was estimated to about one millimetre.

Ventroflexion was followed also by an upward movement of the cord and this was decidedly more extensive than that of the dural sac, as seen by a marked increased tension of the intrameningeal portion of the nerve roots.

Assuming that osteophytes and narrowing of the intervertebral canal has caused a (relative) fixation of the cervical nerve roots, this may reduce the mobility of the cord within the spinal canal. Under such conditions the movements of the head and neck may produce repeated minor traumata to the cord. This may possibly be the cause of the spinal cord damage which was present in the cases discussed here. At an early stage of the illness the cervical spondylosis naturally may cause brachialgia and pains in the leg before the pyramidal damage has become manifest, as seen by reflex changes below the level of the spondylotic lesion.

If this be the background (or part of it) of the myelopathic changes under discussion, we may find it reasonable that the pyramidal tract lesion may be unilateral og bilateral or not present at all, depending upon individual circumstances.

The clinical observations indicate that the pain in the leg seen in cases of cervical spondylosis is of a nature different from the sciatic pain in cases of a lumbar disc lesion. In the cases described in this publication the deep reflexes of the painful leg have been increased, the plantar reflex has been extensor in response and the tone of the painful leg has ben slightly augmented.

As stated above, *Frykholm* explored one of his patients who suffered from both brachialgia and sciatica, there were negative findings regarding the nerve roots L 5 and S 1, and the patient presented no abnormalities of the lower lumbar intervertebral discs. This patient has had no return of the pain in the leg since the decompression of the cervical root 8 years ago when it was observed that the there was a compression of cervical nerve roots only and not of the cord itself.

It should also be pointed out that the patient suffered from pain along the dorsal aspect of the left leg and all the toes, and Dr. *Frykholm* has kindly supplied me with the information that in this patient the Achilles reflexes were equal on the right and the left side. Thus there are several points which distinguish this case of sciatica from the usual case presenting pains in the leg due to a lumbo-sacral root lesion.

The findings in all these cases stand out in contrast to the signs of a peripheral nerve lesion such as are significant of a lumbar root lesion due to a herniation of a lumbar disc.

Such observations point to a tract lesion rather than to a root lesion, which is in agreement with the fact that the pain extended beyond the limits of one or two dermatomes. Frequently the patient refers the pain to the big toe, however, giving the impression that the illness concerns one spinal root only. This may perhaps be explained by the fact that from a developmental point of view a larger number of sensory fibres has been alloted to big toe than to the other parts of the leg and foot.

SUMMARY AND CONCLUSION

The publication concerns the observation that cervical spondylosis giving rise to brachialgia may simultaneously be the cause of pains in the leg resembling sciatica. This may be so even if spondyloarthritic changes are limited to the cervical intervertebral canal.

Cases which have been surgically explored, give evidence of this fact, and cases collected from the literature support the observation.

This type of "sciatica"—*brachialgic sciatica*—differs in nature from true sciatica, as seen in cases of a lumbar disc lesion. The differential diagnostic points have been discussed.

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REINNERVATION OF MUSCLE FIBERS IN PARTIALLY DENERVATED MUSCLES IN THEILER'S ENCEPHALOMYELITIS OF MICE (MOUSE POLIOMYELITIS)

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INTRODUCTION

It was demonstrated long ago (*Mandelstamm* 1882; *Exner* 1884, 1885) that section of one of the two nerves innervating the cricothyreoideus muscle in rabbit will produce no atrophy, whereas severing of both nerves will cause rapid wasting. These observations cannot be explained by a double innervation of the muscle fibers by nerve fibers from both the nerves (*Lederer* and *Lemberger* 1907). Exner discussed the possibility that the denervated muscle fibers after section of one nerve are rapidly reinnervated from the residual nerve.

In 1945 a number of American authors published similar results (*Hines, Wehrmacher* and *Thomson*; *van Harreveld*; *Weiss* and *Edds*). All these authors produced partial denervation of leg muscles in different animals by sectioning spinal nerves and noted a remarkably rapid recovery of the muscle strength. This could not be attributed to hypertrophy of the remaining innervated muscle fibers, nor to regeneration of the severed axons (*van Harreveld*; *Weiss* and *Edds*).

Similar observations have more recently been made by a great number of authors (*Frederick* and *Kosman* 1949; *Hoffman* 1950; *Edds* and *Small* 1951; *Morris* 1953).

Hoffman (1950), *Edds* (1950) and *van Harreveld* (1952) showed that residual motor nerve fibers in partially denervated muscles branch (so-called collateral sprouting) and reinnervate denervated muscle fibers to such a great extent that this mechanism can explain the rapid recovery in muscle strength. This sprouting is found especially in the terminal intramuscular nerve branches (*Hoffman* 1950; *Edds* 1950) but *van Harreveld* (1952) demonstrated also some sprouting in the large intramuscular nerve trunks.

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Recently *Causey* and *Hoffman* (1955) demonstrated extensive collateral sprout formation in large nerve trunks. Substantial bundles of tiny, often submicroscopic fibers were formed, and early stages in the reneurotisation of Schwann cells were demonstrated.

As is well known, the palsies in poliomyelitis have a pronounced regressive tendency in surviving individuals. This spontaneous improvement of paralyzed muscles is generally attributed to recovery of such motor nerve cells, which have been attacked but not destroyed by the virus. To some extent, also hypertrophy of the remaining innervated muscle fibers may occur. It seems reasonable to suggest that collateral sprouting from surviving nerve fibers and end plates may occur in poliomyelitis. *Bowden* (1952) gave a preliminary note on the occurrence of sprouting in poliomyelitic monkeys. She claimed that "there is therefore evidence that the recovery of partially denervated muscle in the experimental animal is due to some extent to extension of the residual motor units".

Recently, *Wohlfart* (1955) and *Coërs* (1955) found regenerative phenomena of motor nerve fibers in amyotrophic lateral sclerosis in man. *Coërs* also reported collateral sprouting in human poliomyelitis.

It is the purpose of this paper to report the occurrence of collateral sprouting in experimental poliomyelitis in mice (Theiler's encephalomyelitis virus).

MATERIAL AND METHODS

125 young white mice inoculated intracerebrally with an intestinal strain of Theiler's encephalomyelitis virus (Mouse poliomyelitis) were studied. We thank professor *Sven Gard* for placing these animals at our disposal.

The animals were killed varying times up to 200 days after paralysis.

The spinal cord was examined at different levels in 86 animals, using Toluidine blue, Einarson's gallocyanine-chromalum and Hematoxyline-eosine stains. In some instances also methylgreen-pyronin and Bodian's silver method were used.

The sciatic nerves were studied in 22 instances, using osmic impregnation or Davenport's silver stain. In 10 cases pieces of this nerve were fixed in buffered osmic solution according to *Palade* (1952) sectioned on a thermal expansion microtome and examined in a Metropolitan-Vickers EM 4 electron microscope.

From each of the 125 mice several pieces from affected muscles were studied with Löwit's gold method, altogether more than 500 muscles. Davenport's silver stain was used for 16 muscles from 10 animals and Gros-Schultze's silver method on frozen sections on 14 muscles from 9 animals. Standard stains, such as Hematoxylin-eosine and Hansen's iron hematoxylin-van Gieson were used on two or more muscles from about half of the animals.

For purposes of comparison the sciatic nerve was transected in 12 normal mice and incompletely crushed in another group of 16 mice. The gastrocnemius muscle of the operated and unoperated side was stained with Löwit's gold method in each instance varying times after the operation.

RESULTS

Observations on the course of the disease in the experimental mice.

Following inoculation there was in this material a latency of 10–30 days before the appearance of paralysis. In most cases the latency was 12–16 days.

During the latency period the animals behaved and looked as usual. The palsies came on acutely, usually reaching a maximum within 1–2 days. The mortality varied with different groups of animals inoculated, on an average being about 20 %. Most of the animals that died did so during the first few days of the paralytic stage.

The day when a visible weakness could first be noted was in this material designated the day of paralysis, even if there was a progression of the weakness on the following day. It is probable that a slight weakness sometimes occurred but passed unnoticed on the day before paralysis. The duration of paralysis given for each animal may therefore suffer from an uncertainty of one and occasionally even two days. This should be stressed and considered when comparisons are made between observations from this material and findings in muscle following complete or partial section of a nerve.

The distribution of the palsies was rather regular but the degree of weakness varied in different animals. The hindlegs were always most severely affected. Sometimes the weakness was confined exclusively to these legs. It should be mentioned, however, that a slight denervation could often be noted microscopically in muscles, which on functional ground had been classified as normal. Thus, often some microscopic denervation was found in the forelimb muscles of animals in which weakness had been found only in the hindlegs. There were, however, also instances of this type with histologically normal forelimb and trunk muscles.

The trunk muscles and especially those of the back were very often visibly affected and frequently the animals suffered from respiratory difficulties. The forelimbs were affected only in the more severe cases and were never completely paralyzed.

Asymmetries in the weakness of the right and left half of the body were sometimes noted, especially in later stages after regression of some of the palsies.

The surviving animals regularly improved to a varying extent. Obvious improvement of the mobility could often be noted one week after the paralytic stage and was regularly noted 2–3 weeks after paralysis, at least to some extent. Some animals with severe paralysis of the hind legs remained almost completely paralyzed in these legs, although the weakness of the forelimbs completely disappeared.

Paralytic muscle groups showed a pronounced atrophy towards the end of the first month. Joint stiffness and contractures often developed in severely paralyzed mice.

Changes in the spinal cord in Theiler's encephalomyelitis of mice.

Only a brief summary of the results of the examination of the spinal cord in Theiler's encephalomyelitis of mice will be given here. The main facts should however be stated as being essential for the interpretation of the changes in muscles and nerves. Further results of the studies on the spinal cord will be published later.

A greater or smaller number of anterior horn cells are completely destroyed during the first day of paralysis. Neuronophagia is frequently found. Many cells show irreversible changes similar to those described by *Bodian* (1948) for the monkey. One finds for instance vacuolization of the cell body or complete dissolution of the Nissl

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Plate 1.

Explanation of figures.

1. Normal mouse. Large ventral horn cells, showing prominent Nissl-substance. (Toluidine blue.)
2. Theiler's encephalomyelitis, 5 days after paralysis. Part of a ventral horn showing cellular infiltration and chromatolytic nerve cell. (Toluidine blue.)
3. Theiler's encephalomyelitis, 9 days after paralysis. A moderately chromatolytic ventral horn cell with intranuclear bodies. (Toluidine blue.)
4. Theiler's encephalomyelitis, 7 days after onset of paralysis. Ventral horn cells, among which the lower two show "central chromatolysis". (Toluidine blue.)
5. Theiler's encephalomyelitis, 9 days after paralysis. The upper ventral horn cell shows "central chromatolysis". (Toluidine blue.)
6. Theiler's encephalomyelitis, 13 days after paralysis. A hyperchromatic ventral horn cell, showing an enlarged nucleolus. (Toluidine blue.)

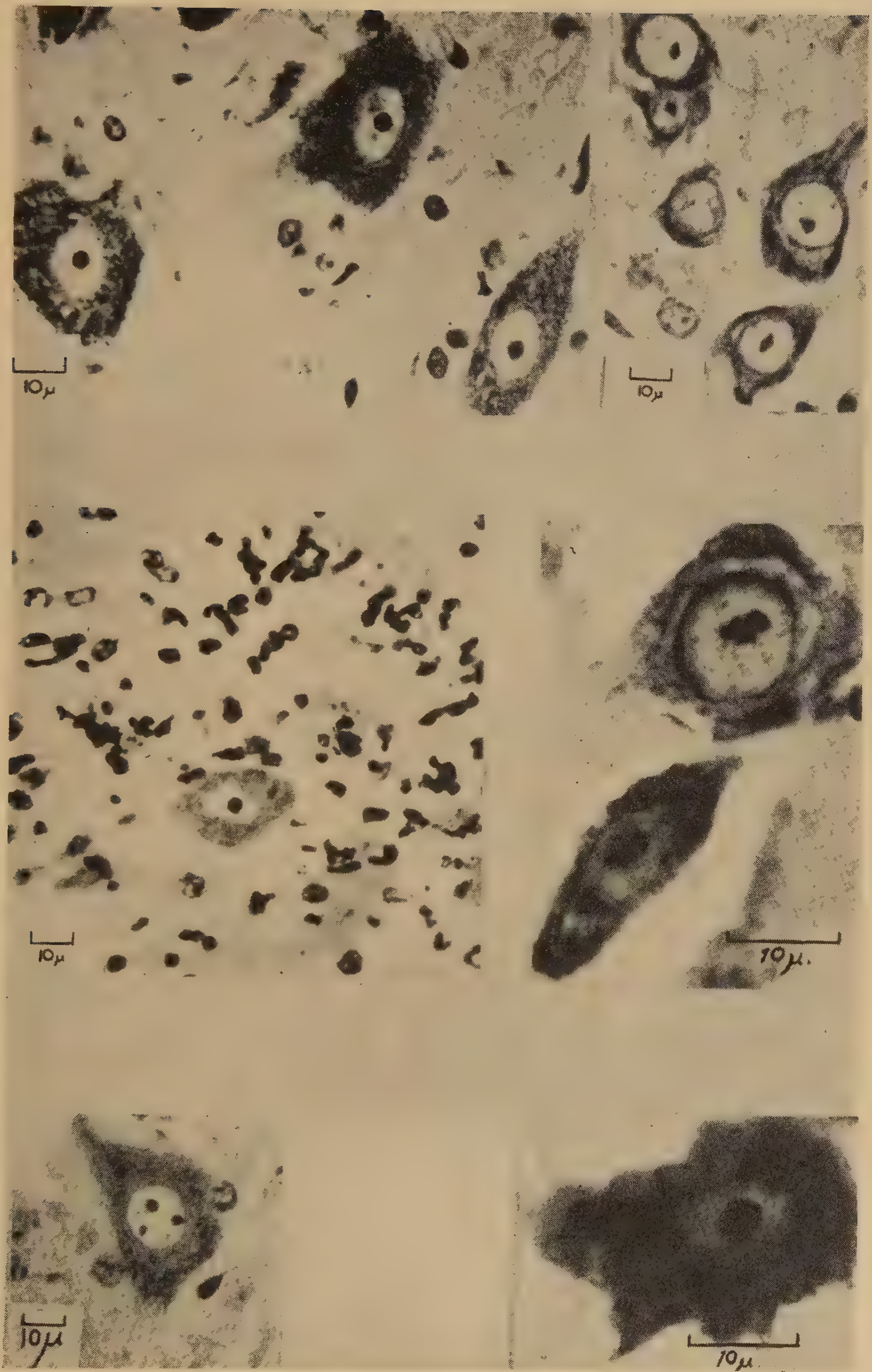
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Plate 1.

bodies with basophilia of the cytoplasm and shrinkage of the nucleus. There is also regularly cellular infiltration of the ventral horns as seen in Fig. 2, slight infiltration of the ventral part of the white matter, usually perivascularly, and meningitis.

The changes are constantly more intense in the caudal parts of the cord than more cranially.

Neuronophagia is occasionally also seen on the second day and groups of cells indicating previous neuronophagia are seen during the first 5–7 days.

Many nerve cells are obviously attacked by the virus, but survive. During the first three days these cells show more or less pronounced chromatolysis and a few such cells can be detected for at least two weeks. Such a chromatolytic neurone may be seen in Fig. 2.

From the 5th day on and regularly until the end of the second week one finds a great number of nerve cells showing "central chromatolysis" (Bodian). Such cells, typical examples of which are seen in Figs. 4, 5, 8 and 9, show Nissl bodies accumulated in the periphery of the cell body and furthermore intensely basophile substance at the nuclear membrane, often in form of a "nuclear cap". Because of the small size of the nerve cells in the mouse central chromatolysis is less striking than in Man or monkey, nevertheless it is easily recognized. Such cells probably represent stages of recovery. Isolated cells with central chromatolysis have been noticed as late as on the 39th day after paralysis.

Normally, the Nissl substance of some of the cells, especially in the lateral part of the anterior horns, stains more heavily than the main bulk of cells. During recovery after poliomyelitis isolated cells are found (Fig. 6 and 9) which must be interpreted as hyperchromatic.

A slight meningitis and some degree of cellular infiltration of the ventral horns is sometimes found even 7 weeks after the onset of paralysis (Fig. 7).

Intranuclear bodies of different size and staining character are com-

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Plate 2.

Explanation of figures.

7. Theiler's encephalomyelitis, 43 days after paralysis. The figure shows the anterior median fissure and part of the spinal cord. There is still a meningeal cellular infiltration and a slight infiltration of the cord. (Einarson's gallocyanine-chromalum.)
8. Theiler's encephalomyelitis, 13 days after paralysis. A binucleate ventral horn cell, showing central chromatolysis. (Einarson's gallocyanine-chromalum).
9. Theiler's encephalomyelitis, 9 days after paralysis. One ventral horn cell hyperchromatic and another shows "central chromatolysis". (Toluidine blue.)

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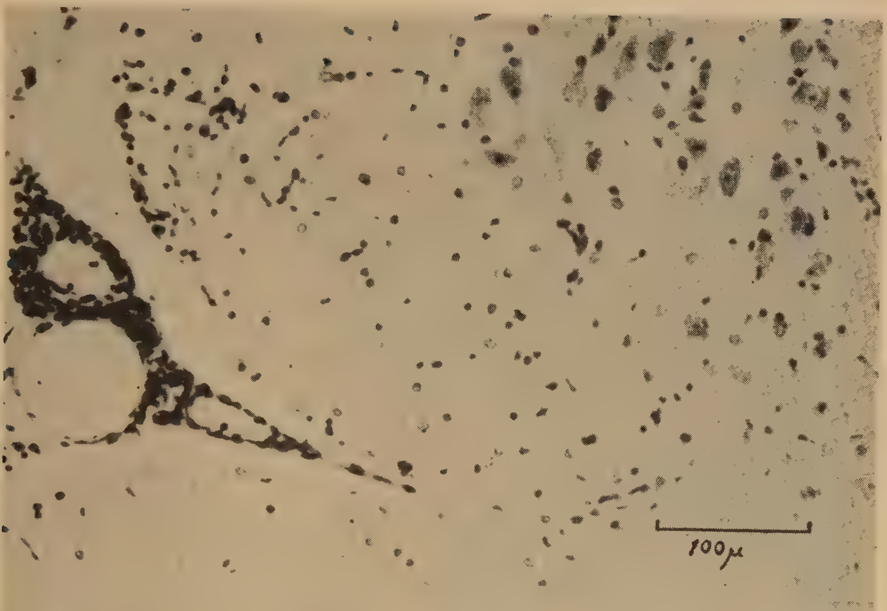

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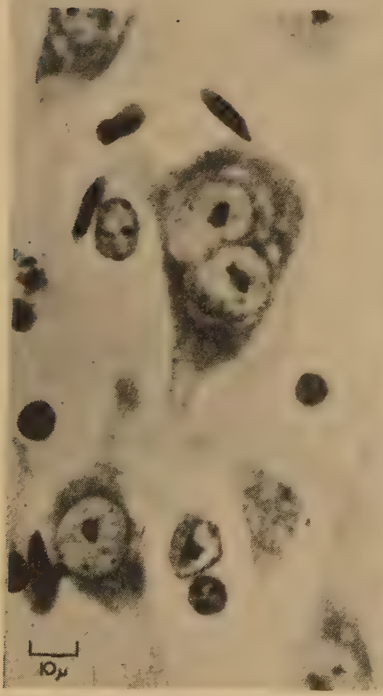

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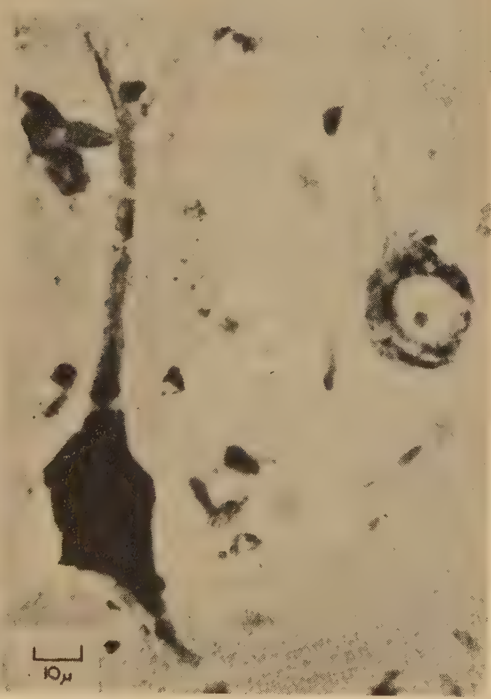

Plate 2.

mon findings from the day of paralysis and for at least 9 days after (Fig. 3). They probably reflect increased activity of nuclear structures and occur mainly in chromatolytic nerve cells. Occasionally, intranuclear bodies have been observed up to 6 weeks after paralysis.

Changes in the muscles and intramuscular nerve trunks in Theiler's encephalomyelitis of mice.

Theiler's encephalomyelitis is as specifically motor as is human poliomyelitis. A more or less massive degeneration of the ventral spinal roots is regularly found but the dorsal roots are always intact. The muscle spindles and Golgi organs and their sensory innervation are always intact, even in otherwise completely denervated muscles.

During the first few days following paralysis there was a progressive Marchi degeneration of a greater or smaller number of fibers in the paralyzed muscles. This degeneration was clearly seen both in gold and silver preparations. The changes in the end-plates were best studied with silver methods. Often on the first day of paralysis and regularly one day later many nerve fibers were in a state of Marchi degeneration and the neurofibrils of the end-plates were broken to pieces, partly dissolved, while parts of the fibrils were thicker than usual. A couple of days later the denervated end-plates in silver preparations were seen as collections of nuclei in connection with nerve fibers in advanced degeneration. Gold staining revealed the denervated end-plates but these were less heavily stained than normally. The cholinesterase stain of Koelle, which was used in some instances,

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Plate 3.

Explanation of figures.

10. Theiler's encephalomyelitis, 9 days after paralysis. Triceps. Gold stained masses (neurosomes) in a denervated muscle fiber. (Löwit gold method.)
11. Theiler's encephalomyelitis, 10 days after paralysis. Intercostal muscle. In the centre a thin sprout (S), following an empty neurilemmal sheath and running to a delicate end-plate at P. (Löwit gold method.)
12. Theiler's encephalomyelitis, 9 days after paralysis. Gastrocnemius. Two surviving motor nerve fibers accompanied by a sprout (S) running to an end-plate (P) on the right. (Löwit gold method.)
13. Theiler's encephalomyelitis, 13 days after paralysis. Gastrocnemius. Three surviving motor nerve fibers with end-plates. A fourth end-plate has recently been re-innervated by a sprout.
14. Theiler's encephalomyelitis, 26 days after paralysis. Quadriceps. Two recently re-innervated end-plates with sprouts (S) in commencing maturation. Another sprout is arising from a node (N) in a surviving fiber.
15. Theiler's encephalomyelitis, 14 days after paralysis. Abdominal muscle. One surviving motor fiber accompanies two degenerated ones. (Löwit gold method.)

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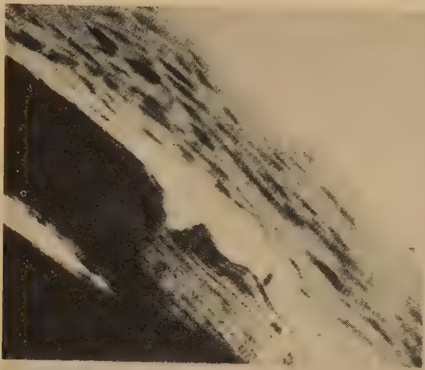

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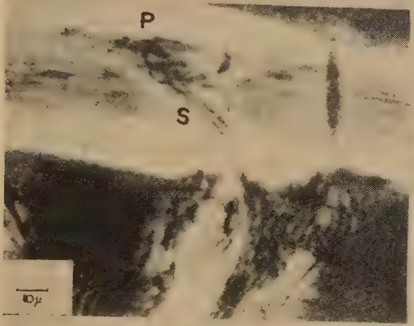

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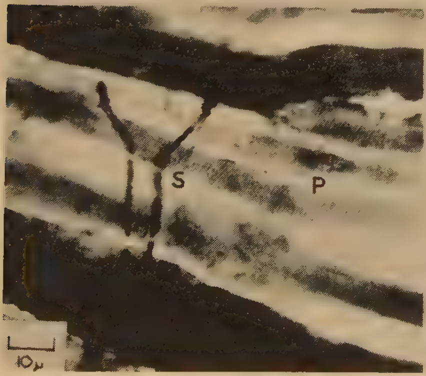

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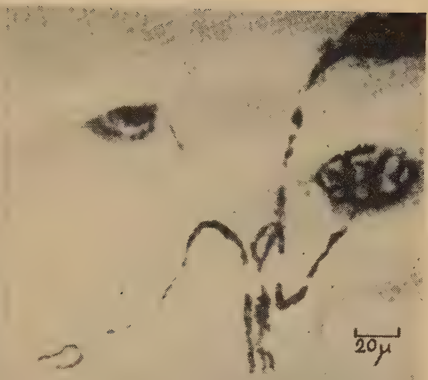

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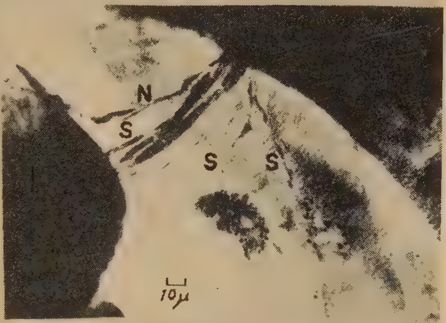

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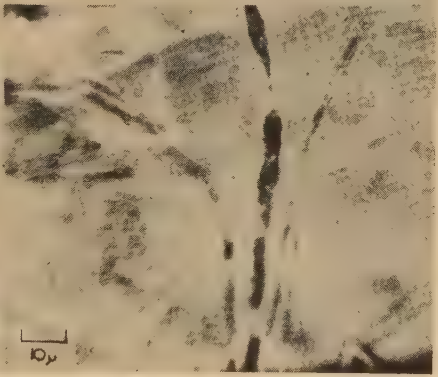

Plate 3.

showed a diminishing stainability of denervated end-plates during the first two weeks, after which they became only faintly stainable. Typical pictures of degenerating nerve fibers and end-plates in Theiler's disease were given by *Wohlfart* (1952) (cf. also Fig. 15).

The denervated muscle fibers, the diameter of which steadily decreased, often contained a great number of gold stained masses ("neurosomes") similar to those described by *Carey* (1943, 1944). Fig. 10 demonstrates a muscle fiber with neurosomes from a poliomyelitis mouse.

As pointed out by *Wohlfart* (1952) small interstitial and perivascular accumulations of round cells were a relatively common finding in paralyzed muscles in the second and third weeks.

A similar cellular infiltration was seen in denervated muscles of mice following transection of the sciatic nerve. A few of the Theiler mice showed however in the second month and later a more pronounced infiltration with round cells with destruction of muscle fibers, indicating a real myositis. The main bulk of animals did not show any such changes, the significance of which remains obscure.

The innervation of normal mouse muscles is very similar to the innervation of the muscles in rat, as described by *Hoffman* (1950), and cat (*Hinsey* 1927; *Tower* 1931; *van Harreveld* 1952).

It is important to point out that the terminal intramuscular motor nerve branches consist exclusively of thick, myelinated fibers, although the larger intramuscular nerve trunks contain also thin myelinated

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Plate 4.

Explanation of figures.

16. Theiler's encephalomyelitis, 14 days after paralysis. Biceps. The figure shows one surviving motor nerve fiber and three thin sprouts (S). The upper and the lower ones run to end-plates (P), which are only faintly stained (typical staining of only recently re-innervated plates). The third sprout is seen arising from a node in the intact fiber. (Löwit gold method.)
17. Theiler's encephalomyelitis, 23 days after paralysis. Gastrocnemius. Two surviving motor nerve fibers (M) and three sprouts (S) are seen. The uppermost sprout is more mature than those of previous figures. (Löwit gold method.)
18. Theiler's encephalomyelitis, 26 days after paralysis. Gastrocnemius. An intramuscular nerve trunk containing a considerably reduced number of thick nerve fibers but many thin sprouts, among which one is seen reaching an end-plate (P). (Löwit gold method.)
19. Theiler's encephalomyelitis, 26 days after paralysis. Gastrocnemius. Two myelinated fibers are accompanied by a thin collateral (S). Another collateral originates from one of the thick fibers—its proximal portion appears to be in commencing maturation. The end-plates are delicate and immature. (Löwit gold method.)

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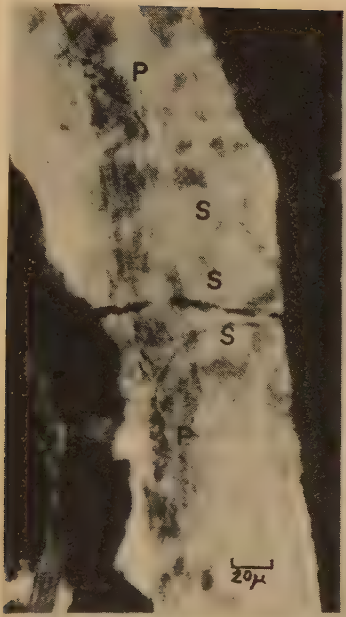

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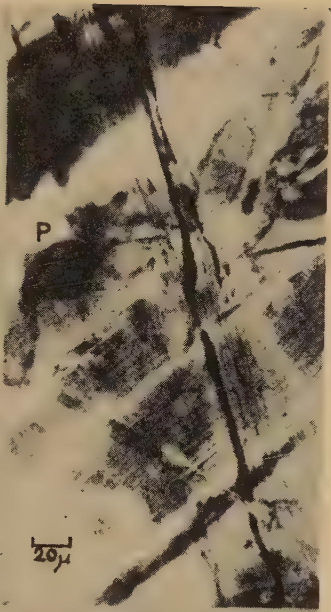

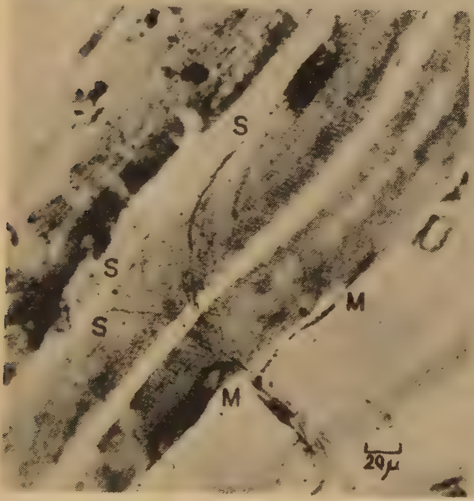

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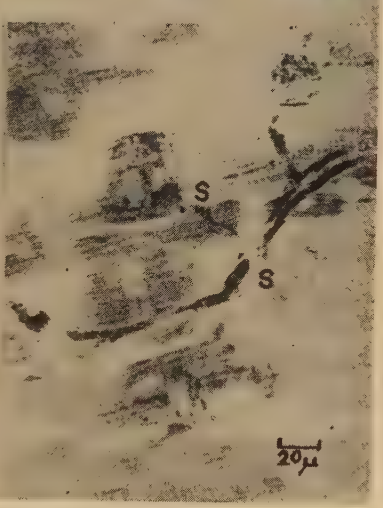

Plate 4.

and probably unmyelinated fibers. The diameter of the terminal motor fibers may vary a little. The sensory fibers of the Golgi organs and the larger type of sensory muscle spindle fibers are the thickest nerve fibers seen in mouse muscles.

During the first few days after paralysis only degenerating or surviving normal nerve fibers could be detected in the Theiler mice. Sprouting in the form of thin, non-myelinated collaterals were found as early as three days after onset of paralysis in one instance, and five days after in another. In general, however, no sprouts were seen up to 8–9 days after paralysis. From the 9th day on after paralysis sprouting could be found to a greater or less extent in every partially denervated, well stained muscle (Plates III–V).

On the whole the sprouts resembled those described by *Hoffman* (1950) and *Edds* (1950) in partially denervated rat muscles. Mouse material has however proved less satisfactory for illustrative purposes: the factor of smaller dimensions accounts for this partly. Illustration has however been complicated also by a tendency for the gold staining to become extremely granular in the crucial period of sprouting.

No out-growing thin fibers were seen in totally denervated muscles. Collateral sprouting was on the other hand often pronounced in subtotally denervated muscle regions, containing only few surviving motor nerve fibers. Fig. 18 demonstrates an intramuscular nerve trunk with only two residual large fibers, but a great number of thin fibers.

When sprouting is found, usually from the earliest time of detection a great number of thin fibers run to end-plates. This must indicate that the out-growth is rapid. These thin sprouts follow empty neurilemmal tubes, as illustrated by Figs. 11 and 22. Sprouts not yet connected with end-plates are rare. They end in a typical swollen tip or occasionally in a ring (Fig. 22).

Many sprouts arise far distally from Ranvier nodes of terminal nerve fibers. Figs. 14 and 16 show this clearly. The larger intramuscular nerve trunks contain however many obvious sprouts but one can rarely see where they originate.

The denervated end-plates, as mentioned above, are less intensely stained by the gold method but are recognizable for several weeks. One gets the impression from this material that the sprouts always re-innervate old end-plates. When re-innervated, they change their staining character: as seen for instance in Figs. 14 and 19 certain points in the sole-plates first stain intensely. Later on the plates increasingly assume the normal appearance.

The newlyformed sprouts are very thin and lack Ranvier nodes (Figs. 12, 16 and 17). In the 3.–4. week they are often seen to have

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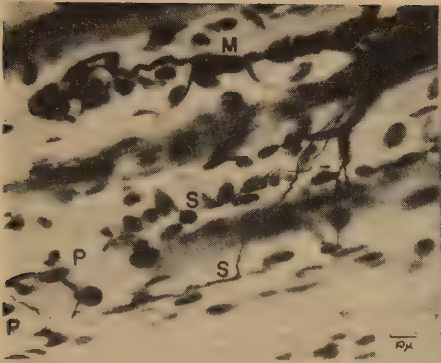

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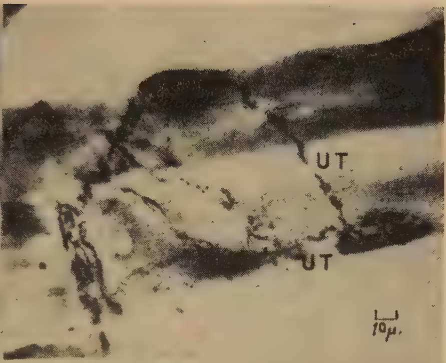

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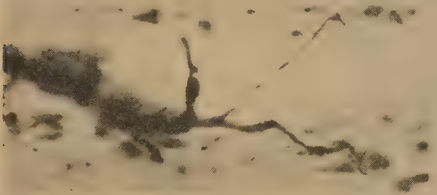

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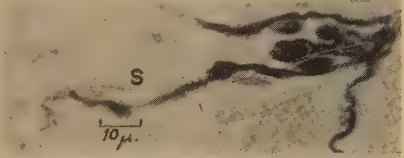

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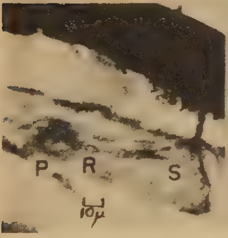

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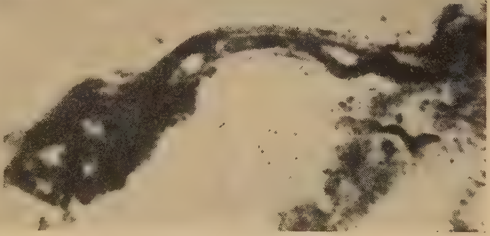

Plate 5.

Explanation of figures.

20. Theiler's encephalomyelitis, 61 days after paralysis. Gastrocnemius. A bundle of nerve fibers, containing normal nerve fibers (M) with end-plates and two thin collateral sprouts (S) with endings (P). (Gros-Schultze silver method.)
21. Theiler's encephalomyelitis, 61 days after paralysis. Gastrocnemius. Collateral sprout emerging from a bundle of surviving fibers and forming a diminutive end-plate. (Gros-Schultze silver method.)
22. Theiler's encephalomyelitis, 9 days after paralysis. Quadriceps. A thin sprout (S) is running within a neurilemmal sheath and ending with a ring (R) close to an end-plate (P). (Löwit gold method.)
23. Theiler's encephalomyelitis, 43 days after paralysis. Biceps. Three end-plates cross-linked by ultraterminal processes (UT). (Löwit gold method.)
24. Theiler's encephalomyelitis, 61 days after paralysis. Quadriceps. A collateral sprout (S) arising from a thick motor nerve fiber and forming a tiny ending. (Gros-Schultze silver method.)
25. Theiler's encephalomyelitis, 33 days after paralysis. Gastrocnemius. Hyperneurotization of an end-plate. One thick and one thinner fiber are seen running within the same neurilemmel sheath to an end-plate. (Löwit gold method.)

matured, either by a diffuse thickening process (Fig. 17) or more irregularly (Figs. 14 and 19). Towards the end of the first month and during the second month one often finds sprouts with a diameter, which is only slightly less than that of normal motor fibers. At this stage it may be difficult to determine whether a certain fiber is a collateral sprout or an unusually thin normal fiber. Obviously a great number of sprouts mature completely and must be assumed to function normally. Just as *Edds* (1950) found in surgically produced partially denervated rat muscles, the terminal innervation ratio—that is the ratio of end-plates to nerve fibers in the terminal nerve branch—increases appreciably in previously paralysed muscles in mouse poliomyelitis. Normally, the number of end-plates in mouse muscles will only slightly exceed the number of terminal nerve fibers but it has been observed in this material that the ratio may reach values as high as 5:1.

In the second month the calibre of the sprouts is most variable. Probably both the maturing process and the time of formation is different for different newly-formed fibers.

In the second month also other phenomena are noticed, namely the hyperneurotization described by *Hoffman* (1952) following surgically produced partial denervation in rats. Fig. 25 shows two nerve fibers running to the same end-plate. This type of finding is not uncommon at this stage and later. The explanation is probably that two different collateral sprouts have reached the same end-plate.

Ultraterminal outgrowth, which is a prominent feature of sprouting

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Plate 6.

Explanation of figures.

26. Theiler's encephalomyelitis, 6 days after paralysis. Electron micrograph of sciatic nerve. A group of surviving, normal myelinated axons (NMA) degenerating myelinated axons (DGA) and newly-formed collaterals (COL) within Schwann cytoplasm (SC): the Schwann membrane (S) is indicated. It will be observed that the few collaterals lying within the Schwann cell tend to adhere to the outer Schwann membrane.
27. Theiler's encephalomyelitis, 16 days after paralysis. Electron micrograph of sciatic nerve. Between the surviving myelinated fibers (NMA) a large number of bundles of collaterals (COL) may be seen, enclosed within Schwann cytoplasm (SC). Again it will be noted that the fibers tend to arrange themselves around the surface of the Schwann cells.
28. Theiler's encephalomyelitis, 7 days after paralysis. Electon micrograph of sciatic nerve. Here only one complete myelinated fiber (NMA) may be seen: The large Svhwann cells contain few collaterals (COL) one of which is senn being enclosed within the Schwann cell in a funnel-shaped invagination (F).

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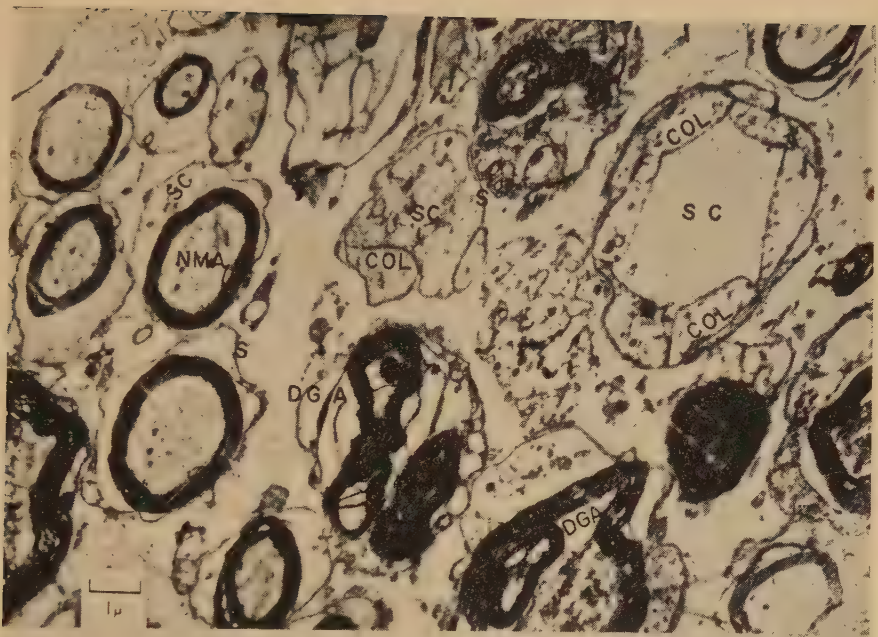
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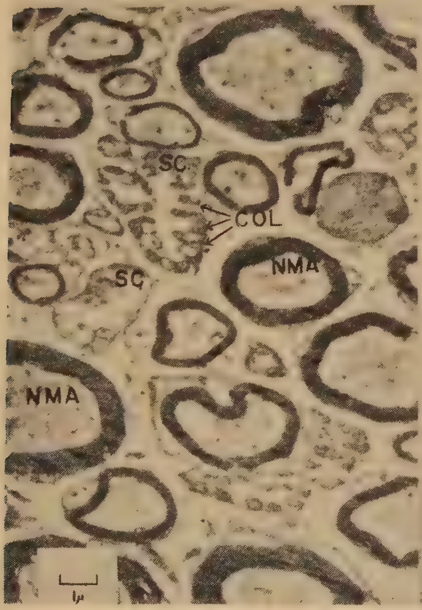
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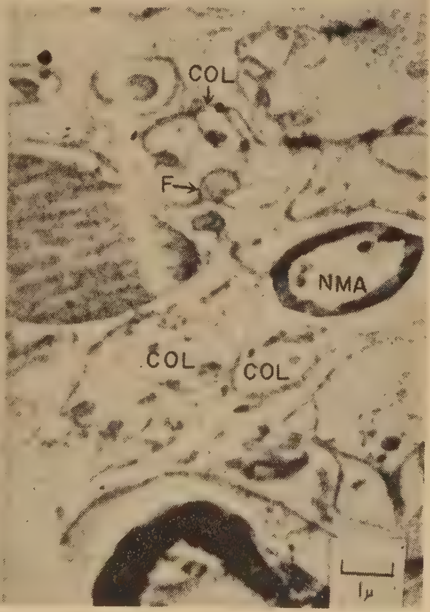
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Plate 6.

in rat muscles—as well as in Man—is very rare in the mouse, both in Theiler's disease and following partial denervation by surgical methods. However, a few instances of its occurrence have been observed, and in several cases hyperneurotized end-plates in the form of two end-plates, cross-connected by an axonal outgrowth, have been detected (Fig. 23).

In some instances a great variation is found in the extent of sprouting in different muscles of the same animal. In one instance, the severely denervated gastrocnemius was found to have been massively re-innervated by fine collaterals—to the extent that a muscle which had been approximately 80 % denervated was now 80–90 % re-innervated. Various other muscles were examined, but although all degrees of denervation were observed, no great amount of sprouting could be observed elsewhere. This variability in sprouting from muscle to muscle is in sharp contrast to the situation, encountered when the denervation is traumatic.

The above observations have been made on gold-stained material. The silver stained sections are less favourable because sections are less useful for following nerve fibers for long distance than are the macerated gold preparations.

In this material silver stained sprouts were observed in one instance 12 days after paralysis. Sprouts were numerous in animals killed during the second month but isolated very thin motor nerve fibers were detected much later, up to 200 days after paralysis. In a section from an animal 32 days after the onset of paralysis it was noted that normal nerve fibers were running to end-plates in atrophic muscle fibers. These end-plates were markedly elongated, resembling those described by *Hoffman* (1950). Collateral sprouts as seen in silver stained sections are to be found in Figs. 20, 21 and 24.

The sciatic nerve was studied in transverse sections in the electron microscope. In this material numerous sprouts were found substantially earlier than in the muscles, consistent with the findings, in partially deneurotised nerves, of *Causey* and *Hoffman* (1955). After the fifth day, in slightly and moderately deneurotised regions of the nerve, small bundles of tiny, non-myelinated fibers, ranging from 0.1 μ upwards, were found scattered amongst the surviving myelinated fibers (Figs. 26–28). The fibers were always enclosed within Schwann cells, as described in the abovementioned paper. In severely deneurotised regions, many degenerating fibers were seen, and numerous deneurotised Schwann cells, undergoing hypertrophy. In some of these, usually around the edges of the cell, a few tiny collaterals could be seen. In some cases these were connected with the Schwann cell membrane by the characteristic ‘mesaxon’ of *Gasser* (1955) but in many instances they were in the process of invaginating into the cell, giving a funnel-shaped appearance (Fig. 28). The impression gained was that many fibers were entering or had recently entered deneurotised Schwann cells.

In general it appeared that very numerous collaterals were formed—but that, at this level, few ever matured very far. Silver stained longitudinal sections supported the occurrence of these collaterals, but succeeded in demonstrating only a proportion of them. Nevertheless tiny collaterals were seen, running along hypertrophic Schwann nuclei.

DISCUSSION

Theiler’s encephalomyelitis of mice was first described by *Theiler* (1934, 1937) and has since been studied by many investigators. The disease has aroused much interest because of its similarity, in many respects, to human poliomyelitis. It is caused by a virus that has been studied thoroughly by several researchers and most exhaustively by *Gard* (1940, 1943, 1944). The histopathologic changes in the spinal cord have been described by *Theiler* (1934, 1937, 1941), *Olitsky* (1939), *Olitsky* and *Schlesinger* (1941) and *Wohlfart* (1952), all of whom stress the similarity between the alterations in Theiler’s disease and those seen in human poliomyelitis. The nature and distribution of the lesions are also very similar to those in mice infected with the Lansing strain of poliomyelitis virus.

In Gard’s paper of 1943 there is a table of all known data about human poliomyelitis and Theiler’s disease as well as of the distribution and properties of the viruses. He concluded that the diseases are analogous.

van Rooyen and *Rhodes* (1949) also classed Theiler’s disease under the heading “The Poliomyelitis Group of Viruses” in their manual of viral infections.

The findings in the spinal cord in the present material, which have been only briefly mentioned, confirm the analogy between Theiler’s disease and human poliomyelitis. Certain aspects of the spinal changes will be studied further and published later.

The muscular changes are during the first few weeks no doubt secondary to the denervation produced by the attack in the anterior horns. There are no signs of a primary virus attack on the muscle. The slight interstitial and perivascular round-cell infiltration, which one often can observe during the first month is of about the same degree and arrangement as that produced by simple section of a motor nerve (*Wohlfart* 1952).

Later on, about from the second month, muscular changes of non-neurogenic origin, caused by over-extension, inactivity due to joint stiffness and so on, complicate the picture. It should especially be mentioned that a few animals showed a rather massive round cell infiltration, mainly perivascularly, during the 2.–6. months. The cause of this "secondary myositis" is obscure. It seems to occur only in atrophic muscles but is often lacking in even more atrophic muscles.

Cellular infiltration of muscles has been observed also in human poliomyelitis (*Hassin,* 1943, *Gifford* and *Dalldorf* 1949, *Denst* and *Neubuerger* 1950). It is unnecessary in this connection to enter a discussion on the relations between poliomyelitis and the Coxsackie virus. In any case, the occurrence of cellular infiltration of muscle both in Theiler's disease and in human poliomyelitis serves to stress the striking analogies between these diseases.

Collateral sprouting was constantly found in this material in partially denervated muscles of all degrees of denervation from 9 days after paralysis. Occasionally it was observed as early as 3 and 5 days after the day of paralysis. Sprouting would appear to commence, according to the electron microscopic evidence, as early in the Theiler infected mice as in traumatised animals. The fact that it cannot be detected by classical neurohistological methods would seem to indicate that diameter does not increase as rapidly, i.e. maturation is delayed. This is supported by the regular detection of distinctly thinner fibers in Theiler infected animals long after the onset of paralysis.

Maturation was often complete one month after paralysis as being recognizable from an increased ratio of end-plates to nerve fibers. On the other hand, a surprisingly large number of thin sprouts were seen still 2 months after paralysis and occasionally thin fibers were observed even 200 days afterwards.

In another series of mice, partially denervated by crushing the sciatic nerve, some sprouting was found constantly 4–5 days after the operation and 6–7 days afterwards the sprouting was tremendous in partially denervated regions. These time relations coincide well with previously published data on surgically partially-denervated muscles from rats. There can be no doubt that the sprouting in Theiler's encephalomyelitis, though striking from 9 days after paralysis, is delayed in its appearance. It seems probable that also the maturation is delayed in many instances. It seems reasonable to suggest that the delay in maturation is causally related to the reversible changes, indicated by chromatolysis, which occur in variable numbers of anterior horn cells in this disease. Since most of these cells recover about a week after the onset of paralysis, it is significant to note that it is during just this first week after the onset that the delay in sprouting is observed. With the restoration of Nissl substance in the anterior horn cells the sprouting appears to accelerate. The observed variation in the extent of sprouting from muscle to muscle in the same animal would support such a hypothesis, and is presumably related to the variation in the extent of reversible virus attack on the nerve cell.

As has already been discussed previously (*Causey* and *Hoffman* 1955) the sprouting in nerve trunks differs somewhat from that occurring in intramuscular nerve bundles. The fibers seldom mature to any extent, as was also found to be the case in the nerves of Theiler infected mice. It seems likely that few of these fibers ever establish terminal connections. It is possible that the totally denervated terminal nerve branches described by *van Harreveld* (1952), which were then invaded by collaterals originating some distance proximally, are a special instance of the generally occurring sprouting in large nerves. Such proximally-formed sprouts were also encountered in this study, and it seems likely that the sprouting occurs at all levels distal to the point of admixture of degenerating and intact fibers, in this case anywhere along the length of the motor pathways. Whilst these collaterals probably become functional in only a small percentage of cases, their occurence clarifies the general pattern of events.

The occasional detection of a hyperneurotised end-plate usually in the form of two end-plates cross-linked by an ultraterminal process is of especial interest, in that such structures are never encountered in normal material. Although it was earlier interpreted as being due to the regeneration of the originally interrupted axon (*Hoffman* 1952) it seems more likely in this instance to result from a collateral entering the same (originally denervated) end-plate as has an ultraterminal process.

SUMMARY

1. Paralysis ensued in Theiler encephalomyelitis-infected mice after a delay of ten to thirty days. After varying periods, and to differing degrees, motor function returned to the paretic muscles.

2. The spinal cords showed destruction of anterior horn cells in the first days after infection, followed by chromatolytic reactions in many more motor cells.

3. Sprouting of new branches from surviving motor fibers within the muscles was observed, being significantly delayed in comparison with collateral sprouting initiated traumatically. The amount of restoration

of motor innervation varied from muscle to muscle, and from animal to animal, correlating fairly well with the observed improvement in muscle function.

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ADRENOCORTICAL AND THYROID FUNCTION IN PERIODIC CATATONIA

By

LARS-M. GUNNE and CARL A. GEMZELL

With his review, published in 1953, *Gjessing* has given the last touch to the work on periodic catatonia that he began in the twenties. In a selected material of schizophrenics, with regularly recurring periods of stupor or excitement, he made continuous recordings during several years of, among other things, the nitrogen balance, the basal metabolic rate, and the urinary excretion of electrolytes. He found certain regularly reappearing variations in connexion with the carefully registered psychotic periods. Some of these findings may be interpreted as indications of changes in the hormonal system of the patients.

Gjessing, as well as some other investigators, has suggested the possible existence of changes in the function of the thyroid or the adrenal glands in patients with periodic catatonia. *Gjessing* was of the opinion that the thyroid function might be defective. The basal metabolic rate is often lowered to subnormal values during the intervals between the psychotic periods, whereas in the reaction phase the oxygen consumption rises to levels even higher than normal. During the intervals there are also other clinical signs of hypothyreosis. The therapeutic results with thyroid hormone may also support the theory of a defective function of this gland.

Gornall et al. (1953) estimated the serum protein-bound iodine (PBI) in one case of periodic stupor. They found a constant level of PBI, while the basal metabolic rate increased during the disturbed phase.

Gjessing's results, which show periodic fluctuations of the water and electrolyte metabolism and the carbohydrate metabolism, indicate that the adrenal gland may play a part in different phases of the disease. *Rowntree & Kay* (1952) investigated two cases and found an increase in the urinary 17-ketosteroids at the peak of the period of excitation. They also gave indirect evidence that the mineral corticoids were dominating just before the disturbed phase and the glucocorticoids during the remission. *Gornall et al.* noticed in one case a slight reduction of the urinary 17-ketosteroids during the disturbed periods, while in another case there was a remarkable increase of urinary corticoids as well as 17-ketosteroids. The latter case showed a normal increase of the steroids after ACTH-stimulation, while the former had a defective adrenal response.

Thus, the limited material collected from the literature shows that the behaviour of the adrenal steroids during the periods of psychosis varies from one case to another. The interpretation of these results has been discussed by many authors without their giving any laboratory observations of their own (*Lewis* 1947, *Lindsay* 1948, *Danziger et al.* 1953, 1954).

In this paper a report is given of two cases of periodic catatonia whose condition was followed by determinations of 17-hydroxycorticosteroids in the plasma, eosinophil counts, and the plasma concentration of protein-bound iodine. Variations of the nitrogen balance were studied by serial determinations of non-protein nitrogen (NPN), as described by *Gjessing* (1938, 1953) and *Mall* (1951).

METHODS

Two patients were investigated. Only one proved to belong to the group of genuine periodic catatonics (according to *Gjessing*: syntonous-synchronous reaction type C). In the other patient electroshock and insulin therapy had caused pseudo-periodicity in an almost aperiodic case (asyntonous-asynchronous reaction type).

The level of 17-hydroxycorticosteroids in plasma was determined according to the method of *Nelson* and *Samuels* (1952). Approximately 10 ml of heparinized plasma was extracted with chloroform. Chromatography was carried out on magnesium silicate-Celite columns. The micro-modification of the colour reaction of *Porter* and *Silber* (1950) was used for quantitative determination. Correction for background absorption was made by using the colour correction equation by *Allen* (1950). All the levels of 17-hydroxycorticosteroids were expressed in terms of μg per 100 ml of plasma. The average plasma level of 52 normal males and females at 8 a.m. was 11.5 ± 0.95 μg per 100 ml of plasma (*Gemzell et al.* 1955). The error of a single determination was $\pm$ 1.9 μg per 100 ml of plasma, and the coefficient of variation was $\pm$ 12 per cent.

The function of the adrenal cortex was investigated by means of an "ACTH test". Fifty mg of a long acting ACTH preparation (ACTON-Prolongatum, Nordiska Hormonlaboratoriet) was given as an i.m. injection at 8 a.m. on two successive days. The plasma levels of 17-hydroxycorticosteroids were estimated before each injection and 8 hours later. Normally, the plasma levels rose and reached a maximum of about 40 to 60 μg per 100 ml of plasma on the second day at 4 p.m. No increase, or an increase not exceeding 20 μg per 100 ml of plasma, indicated a poor function of the adrenal cortex (*Gemzell* and *Franksson,* 1953, *Gemzell,* 1956).

The amount of 17-ketosteroids in urine was determined by the method of *Callow, Callow* and *Emmens* (1938) with the modification of *Vestergaard* (1951). The 17-ketosteroids were expressed in mg per 24 hours. According to *Hamburger* (1948) the average excretion of urinary 17-ketosteroids in normal men, 30–50 years old, is 10–15 mg per 24 hours.

The eosinophil counts were performed by the method of *Rud* (1947).

The protein-bound iodine (PBI) was determined by Dr. G. Widström, Stocksund, according to a method described by *Barker* and *Soley* (1951).

In one case the effect of large doses of thyroxine upon the adrenal cortical function was investigated.

CASE REPORTS

Case 1. C 16/53. Born in 1903. Habitus pychnicus. Normal somatic functions. Diffuse vitiligo on the extremities.

His father was probably an alcoholic. No other nervous or mental illness in the family. Passed elementary school and military service with good marks. Worked as a businessman on his own for several years. Since 1930 employed at a printer's shop, where he was very diligent and made himself appreciated by his fellow workers. No particular difficulties in his psychosexual development. Has taken some interest in religion and is now in the Good Templar organization. Unmarried.

He was quite well until about 40 years of age. Due to depressive periods he went to a psychiatrist for the first time in 1942 on his own initiative. In August 1943 he was for the first time admitted to a mental hospital (Beckomberga sjukhus). He was regarded as a case of catatonic schizophrenia.

He was repeatedly treated with insulin and electroshock and seemed to improve temporarily by this therapy. Soon, however, he relapsed. In the spring of 1949 the symptoms decreased and he was discharged in April 1949. During the next three years he was quite well and able to take care of himself. In April 1952 he was again admitted to the hospital. On admission he was in elevated spirits and talkative, but incoherent, with disorganized thinking and hallucinations. He sang, laughed, and cried that he was a nightingale. Before he was taken charge of, he was very troublesome in the house where he lived. He intruded upon his neighbours, threw money out of the window and was running about half dressed. Following treatment with subcoma doses of insulin he was again discharged in June 1952, free from symptoms. In the spring of 1953 he was ill again several times at intervals of two months, each time readmitted in a state of violent excitement, yelling and singing loudly. Since he later proved to have exactly one episode a month, it is possible that during this time, the insulin and electroshock therapy may have abolished every second period.

In June 1953 a continuous registration according to *Gjessing* (1935) was started. Every day a subjective assessment of the patient's psychical state was made according to a special ten-grade scale for mood, motor activity, and capacity of concentration. The temperature, pulse rate, body weight, and hours of sleep at night were also recorded.—The curves thus obtained agreed quite well with *Gjessing*'s typical cases.

The first periods registered appeared as slight dysphoric retardations. Gradually, however, the intensity of the attacks increased, and from the autumn of 1953 he had catatonic periods of violent excitement occurring regularly once a month and each time lasting for a fortnight. Each period was preceded by slight dysphoria: the patient felt listless, thought that he was going to have a cold, seemed morose, apathetic, and withdrawn. After three days the change suddenly occurred: he seemed more and more anxious and restless for some hours with increasing talkativeness; then suddenly there was an outburst of excitement. In the middle of a conversation he would jump to his feet, shout and sing, throw his clothes off, begin to cast things around, and he had to be isolated. Then he nearly always tore his mattress, soiled with his urine and excrements and seemed to be violently affected with hallucinations. Sometimes he also behaved belligerently towards the nursing staff. After a week some decrease of the excitation was noticed and during the next few days the patient rather rapidly recovered his habitual state. During the intervals he was calm and orderly, good-humoured, nice and helpful. He took up some hobbies such as painting, and made himself useful in the ward.

TABLE 1

A comparison between some clinical observations and laboratory results during psychotic phases and intervals (Case 1).

	Psychotic phase	Interval
Temperature	Elevated	Normal
Pulse rate	Increased	Decreased
Duration of sleep	Reduced (0–6 hours)	Normal (8 hours)
Body weight	Decreased	Increasing
Plasma NPN	Low	Increasing
Plasma PBI	Constant (normal)	Constant (normal)
Plasma 17-hydroxy-corticosteroids	Increasing during the first 3 days, then low	Increasing
Eosinophils	Low the first 3 days, then high	Constant
Urinary 17-ketosteroids	Decreasing	Increasing

In Table 1 are summarized the findings during two observation periods of 7 months altogether. During this time the patient was kept on a constant diet of

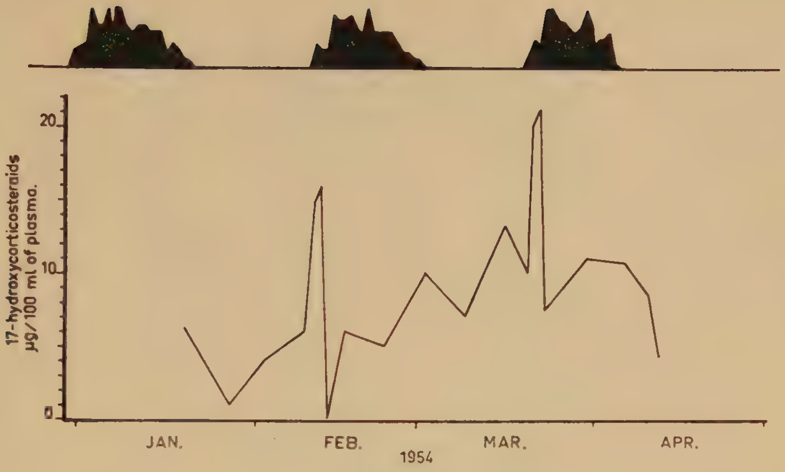

Fig. 1.
Correlation between the psychotic phases and the plasma level of 17-hydroxycorticosteroids (Case 1).

14 g of nitrogen daily (mixture of milk, cream, eggs, sugar, salt, and vitamins). During the first period of examination in the summer of 1953 the psychotic episodes were moderate, and 24-hour samples of urine could be collected. This was not possible during a later period of investigation in the spring of 1954. Between these two periods of observation an attempt at alleviation of the condition was made with small doses of thyroid (Laevoxin, Nyegaard, 0.3–0.4 mg/day). According to *Danziger et al.* the length of the thyroid administration is important for the results of the treatment. One hundred days of treatment was considered a complete course. The thyroid treatment, however, was not effective in abolishing or moderating the psychotic periods. The doses were maintained so high, in accordance with several investigators, that the BMR was raised above + 15 per cent, even during the intervals. As long as the treatment lasted, the periods of illness and the free intervals were shorter. When the thyroid therapy with small doses had definitely failed, and the treatment was discontinued, the periodic rhythm became slower, and the disturbed phases lasted 5–6 days longer.

Figure 1 shows the correlation between the periods and the plasma levels of 17-hydroxycorticosteroids. A remarkable increase in the steroid level occurred during the first, few, dysphoric days of each period, followed by a sharp drop when the period turned into its catatonic excited phase on the 4th day.

Figure 2 shows the various clinical and laboratory data in March 1954, during the patient's last psychotic period. After this time a spontaneous remission occurred. The top of the diagram shows the psychic state registered by subjective assessment. Beneath is an objective record of the periods by the aid of EEG. One type of EEG was found during the interval and a different type at the peak of the excitement. The figure shows that the EEG alterations appeared a few days later than the psychic changes and returned (via intermediate types) to the interval type some time after the period was over. The EEG findings will be analyzed in detail elsewhere (*Gunne & Holmberg*, 1956). After this last period a few abortive periods were recorded by EEG. They appeared at the regular time, but were not accompanied by any clinical symptoms.—Below the EEG curve are the data for PBI and basal

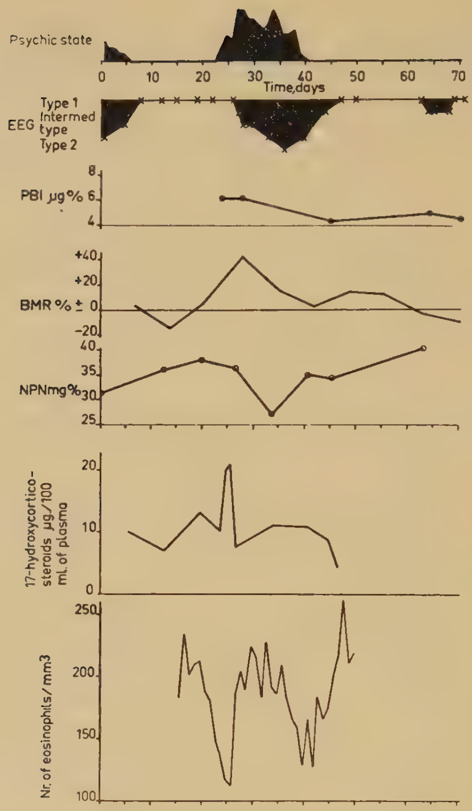

Fig. 2.

Correlation between the psychotic phase and the EEG, plasma level of protein-bound iodine (PBI), basal metabolic rate (BMR), plasma levels of non-protein nitrogen (NPN), plasma levels of 17-hydroxycorticosteroids and number of eosinophils (Case 1).

metabolic rate (BMR). While the BMR rises during the period, the PBI is practically constant. Non-protein nitrogen decreases during the period from 38 to 27 mg per cent, which, as the patient was kept on a constant diet, may indicate a nitrogen retention. The plasma levels of 17-hydroxycorticosteroids and the number of eosinophils are at the bottom of the figure. Following the eosinopenia during the first few days of the periods, there used to be a marked rise in the eosinophils (to about 600/mm^3). This time, however, the eosinophilia for unknown reasons failed to appear.

In April and June 1954, ACTH tests were performed. Neither a significant rise of the plasma levels of 17-hydroxycorticosteroids nor any decrease of the eosinophils was obtained. (See Fig. 3.)

The patient was discharged from the hospital in June 1954 soon after the second abortive period.

Case 2. F 223/52. Born in 1922. Athletic habitus. No mental illness in the family. His health had previously been rather good. In August 1952 he had an episode of

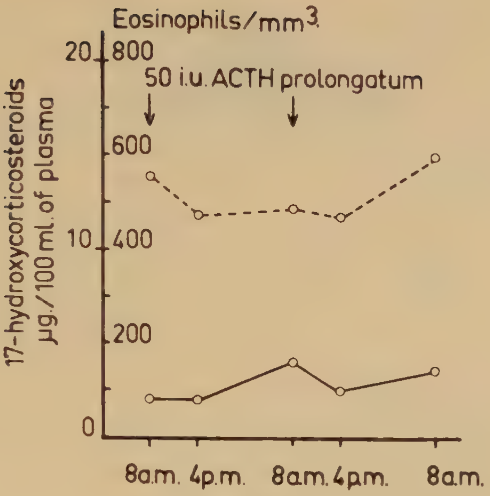

Fig. 3.

Plasma level of 17-hydroxycorticosteroids (solid line) and number of eosinophils (dotted line) following two intramuscular injections of a long acting ACTH preparation (Case 1).

catatonic excitement and was admitted to Beckomberga Hospital, where he has since been treated under the diagnosis of schizophrenia. He was submitted to a very intense treatment according to the usual methods with repeated insulin coma and electroshock series. In January 1953 an attempt was made at cortisone treatment. During these various treatments his state of mind was vacillating between a rather quiet phase when he seemed relaxed and able to carry on an orderly conversation (though probably never quite free from hallucinations) and an intense catatonic excitement with impulsive acts of violence, autism, massive hallucinations, paramimias and other types of stereotyped behaviour, refusal to eat, untidiness, etc. Now and then the excited state was transformed into a few days of stupor with complete mutism. The periods of excitation were of different length, varying from outbursts of two days to periods of 41 days. The repeated treatments brought about remissions of varying length from 11 to 57 days.

In January 1954 the investigation was started, and all treatment was discontinued. In the spontaneous course that followed, the symptomless intervals became very short and never exceeded four days[1]. After a couple of rather distinct periods of excitation the patient gradually entered a stage of more and more diffusely defined psychotic episodes. Since the spring of 1954 he has been mostly in a state of shyness and autism, tension and unreliableness, hallucinations and delusional thinking. The intensity of the symptoms has shown some slight variations, but no regular periodicity could be observed, nor did the pulse rate, temperature, body weight,

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[1] The following scale was used in rating the clinical state of this patient: Stage 1. Tense, taciturn, curt in manner, irritable. Stage 2. Hyperactive, manneristic, deluded, talking to himself. Stage 3. Talking very loudly, often incoherently, occasionally shouting, moving hastily, destructive. Stage 4. Yelling, singing, cursing and swearing, banging the door or walls, belligerent. Stage 5. Semistuporous.

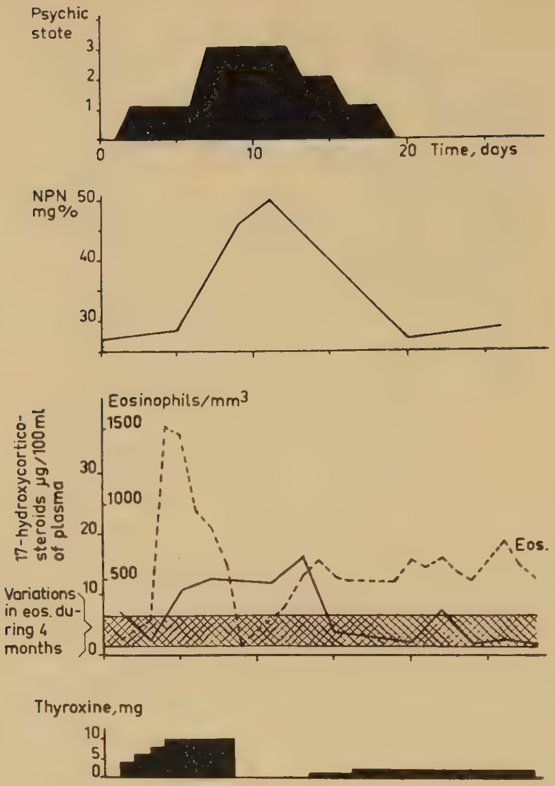

Fig. 4.

Effect of intramuscular injections of thyroxine (68 mg) on the plasma levels of 17-hydroxycorticosteroids (solid line) and the number of eosinophils (dotted line) (Case 2).

and non-protein nitrogen show any regular periodic deviations (in *Gjessing*'s terminology: asyntonous-asynchronous reaction type).

Eosinophils were counted every morning and the 17-hydroxycorticosteroids were estimated at 8 a.m. once a week. The eosinophils varied from a minimum of 80 to a maximum of 250 during four months of investigation (in Fig. 4 these variations are represented by a shaded area, for comparison). The plasma levels of 17-hydroxycorticosteroids did not show any correlation with the vaguely defined psychotic episodes. A few times during the summer of 1954 the plasma levels of the steroids were elevated (values of 30–32 µg per 100 ml of plasma) with no observable change in the psychic state, but for the most part the level was low 2–4 µg per 100 ml of plasma). Administration of ACTH gave no increase in the plasma levels of 17-hydroxycorticosteroids (Fig. 5). The plasma level of PBI was normal and showed no correlation with the mental variations.

Although the case did not prove to be a genuine periodic catatonia, an attempt at alleviation of the condition was made with large doses of thyroxine (Inj. thyroxine Roche) in December 1954. Sixty-eight mg were injected intramuscularly over an 8-day period. The treatment was started when the level of non-protein

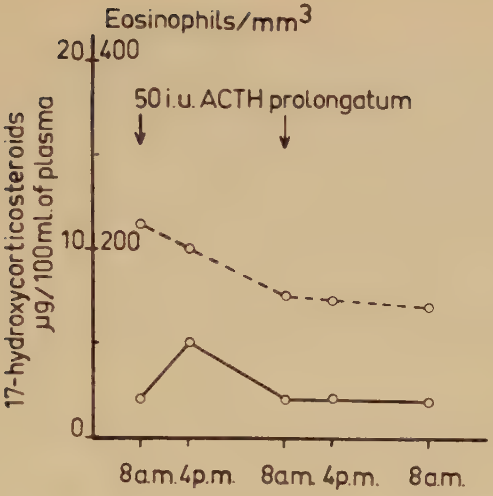

Fig. 5.

Plasma level of 17-hydroxycorticosteroids (solid line) and number of eosinophils (dotted line) following two intramuscular injections of a long acting ACTH preparation (Case 2).

nitrogen was low and could be expected to rise. During the first five days of treatment the NPN remained unchanged and the patient was calm and remarkably unaffected by the treatment. On the fourth day the eosinophil count rose rapidly from a constant level of about 100-150/mm^3 up to 1500. Finally, on the sixth day, as the patient entered into a phase of violent excitement, the NPN rose rapidly to 50 mg per cent, indicating an intense nitrogen excretion. The plasma level of 17-hydroxycorticosteroids, which was low at the beginning of the treatment, now showed a slight increase, and the eosinophils were, within a few days, reduced from 1500 to 60/mm^3. After the short and moderate rise the plasma steroids returned to their previous low level. Following a continuous oral thyroid administration the eosinophils stayed on a higher level than before (300–500/mm^3) (Fig. 4).

After this treatment the patient had an interval of 6 weeks free from symptoms, which was the longest quiet period since the beginning of the investigation. After that he entered into a new psychotic period.

DISCUSSION

In the two cases reported the results of this study seem to furnish some evidence for a disturbed function of the adrenal cortex. Following stimulation with ACTH the adrenals do not respond normally, but rather behave as in a case of Addison's disease. It may be possible to activate the adrenal cortex, but the amount of ACTH necessary for this activation seems to be much larger than the amount necessary for a normal person with intact adrenals. Generally, the average morning levels of 17-hydroxycorticosteroids in the plasma of these patients are low, but such low levels are quite often found in the plasma of perfectly normal individuals as well. However, in both patients the plasma values of 17-hydroxycorticosteroids occasionally increased to an elevated level showing that, in spite of the poor response to exogenous ACTH, the adrenals were capable of responding to endogenous stimuli. These findings are in good agreement with earlier reports concerning urinary steroids in schizophrenic patients (*Pincus* and *Hoagland* 1950, *Reiss et al.* 1949). On the other hand *Bliss et al.* (1955), studying plasma 17-hydroxycorticosteroids, found no difference in the adrenal cortical response to intravenous ACTH in normal persons and schizophrenics.

In our typical case of periodic catatonia the activation of the adrenal cortex was observed during the first few days of the disturbed phase. As the period turned into its catatonic excited phase on its fourth day, the plasma steroids suddenly dropped to a low level. The non-protein nitrogen level followed the same direction, though with less marked excursions.

In the second case with an aperiodic schizophrenia, no correlation was observed between the vaguely defined changes of the psychic state and the plasma steroids, which, though generally low, on a few occasions showed unexpectedly high levels. Nor did the minute changes of NPN show any constant relation to the psychic picture.

The concentration in the plasma of the PBI did not show any marked changes in connexion with the psychotic periods, while in our typical case of periodic catatonia, the BMR rose considerably (to + 54 per cent) during the disturbed phases. Thus, we have found no proof that the variations of the nitrogen balance should be caused by a change in the thyroid function. It seems more probable that changes in the adrenal cortical function might cause the variations in the nitrogen balance. To confirm such an assumption it would be necessary to investigate a greater material.

When unphysiologically large doses of thyroxine were administered there was a certain increase of the plasma steroid level. This increase, however, was not very high and did not reach its maximum until a week after the thyroid therapy had been instituted. As an interesting subsidiary effect during the thyroxine administration a sharp rise of the eosinophils appeared before any effect on the 17-hydroxycorticosteroids was noticed. A certain eosinophilia has been reported by *Mall* (1951) in the third to fifth week of thyroid treatment. The nature of this rapidly passing eosinophilia in our case is obscure. Whether it represents a direct effect of the thyroxine on an organism with slow adrenal function, will be the subject of further study.

SUMMARY

A case of periodic catatonia (Case 1) and a case of aperiodic schizophrenia (Case 2) have been investigated during a period of about one year. The plasma levels of non-protein nitrogen (as a measure of the nitrogen balance), 17-hydroxycorticosteroids, and protein-bound iodine were estimated with special regard to a possible change in the function of the thyroid or adrenal glands.

1. Case 1 showed distinct periodic deviations in the level of 17-hydroxycorticosteroids synchronously with the disturbed phases. The maximum value of the 17-hydroxycorticosteroids occurred during the first three days of the disturbed period before the real catatonic excitement had started.—Case 2 showed no such periodic changes.
2. Case 1 showed an increase of the non-protein nitrogen just before the disturbed period and a reduction (nitrogen retention) in the middle of the period.
3. The plasma levels of protein-bound iodine were fairly constant in both cases and within normal limits.
4. In both cases the adrenal cortex gave a poor response to ACTH.
5. In Case 2 thyroxine treatment was followed by a rapidly passing eosinophilia.

The significance of the findings is briefly discussed.

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ENURESIS

I. *A Study with Reference to the Morbidity Risk and Symptomatology*

By

BERTIL HALLGREN

INTRODUCTION

In the present study enuresis is defined as repeated involuntary micturition after the fourth year of life in the absence of gross organic lesions of causal significance.

Some authors, e.g. *Crosby* (1950), differentiate between "essential enuresis" and enuresis caused by mental disturbances. It is very difficult, however, to decide in a given case whether the mental disturbance present is causally related to the enuresis. Accordingly, opinions stated in the literature as to the frequency of such a causal connection show considerable disagreement. One of the objects of the present survey is to study enuresis with regard to the occurrence and importance of certain mental factors. I therefore disregarded these factors in the definition of enuresis. A special problem is raised by the most severe grades of mental defectives who are, as a rule, incapable of learning vesical control. This group, however, is not represented in the present series. which consists of children attending elementary schools.

The choice of four years of age as the borderline between enuretics and non-enuretics is of course arbitrary. Many authors—*Stockwell & Smith* (1940), *Kanner* (1948), *Bakwin & Bakwin* (1954) and others—put the borderline at three years, others, e.g. *Crosby* (1950), *Hodge & Hutchings* (1952), at five. The average child is expected to keep

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his clothes and bed clean at about 2–3 years of age—cp. *Gesell & Ilg* (1943), *Despert* (1944), *Kanner* (1948), *Wallgren* (1949), *Klackenberg* (1955). The time varies widely, however.

The main purpose of the present survey is to provide a rough estimate of the morbidity risks of nocturnal and diurnal enuresis, respectively, for a subsequent clinical and genetic study of enuresis to be based on a clinical material. (This study has just been completed and will be published in a later issue of this periodical). Such information is of major importance for a genetic-statistical analysis. In the literature I have found no reliable figures secured by random sampling, as to the morbidity risks of nocturnal and diurnal enuresis, as defined in the present study, in boys and girls. The morbidity risk figures given by different authors vary widely. Therefore I considered an investigation of the morbidity risk of enuresis with a representative material a matter of some urgency. The objects of the present study are the following:

To estimate the morbidity risk figures for nocturnal and diurnal enuresis in a representative series of children attending elementary schools.

To make an analysis of the series of enuretic children thus selected with regard to the symptomatology of enuresis.

In a following issue of this periodical—cp. *Hallgren* (1956)—the material will be analysed with regard to certain physical, mental and social factors possibly of importance as causes of enuresis or otherwise associated with it.

MATERIAL AND METHODS OF INVESTIGATION

The investigations were carried out during the later part of the autumn term 1953. The material was collected as follows.

First-form pupils of municipal elementary schools in Stockholm were selected for investigation, those schools being preferred in which the children had passed an obligatory intellectual maturity test. In this manner information was obtained as to the intelligence of the children, operationally determined on the basis of a group test.

In planning the study it was my intention to secure a material representing a random sample of the average elementary-school population. I therefore chose schools—9 in all—serving city districts as well as newer and older suburban settlements and admitting different social groups. However, there was a statistically significant *** difference in the distribution according to social group between the present material and the population of Stockholm (see Table 1). In the present series

TABLE 1

Distribution of the Material According to School and Social Group.

School	Social group I	II	III	Total
Hökarängen	20	138	236	394
Midsommarkransen	10	50	131	191
Björkhagen	47	121	86	254
Norra Ängby	29	55	49	133
Bällsta	5	19	55	79
Abrahamsberg	54	96	67	217
St. Essingen	23	51	44	118
Engelbrekt	60	42	29	131
Hjorthagen	—	19	49	68
Matteus	37	58	75	170
Hedvig Eleonora	90	93	54	237
Total	375	742	875	1,992
Stockholm according to the 1952 election statistics	18,448	69,689	74,647	162,784

there is an over-representation of families belonging to Social Group I. The difference in the percentage distribution among the three social groups is not large, however, the figures being 18.8, 37.3 and 43.9 in the present material and 11.3, 42.8 and 45.9 in the population.

The social grouping is in accordance with that adopted in the Stockholm Official Election Statistics of 1952. Social Group I includes the so-called upper classes, Social Group II the middle classes and Social Group III the working classes. The children included in the present series were grouped according to the occupation of the father or stepfather, even if they were brought up by mothers who were divorced or widowed. In a few instances—2 altogether—where bith was illegitimate, the cases were grouped according to the mother's occupation.

The social group to which the case was assigned was based on the records of parental occupation kept by the schools. In some cases where these records were incomplete, the data were checked at the Inland Revenue Office of the City of Stockholm (*Stockholms stads skatteverk*).

The distribution according to social group of the Stockholm population was ascertained from the Election Statistics of 1952. In order to render the two series more comparable, I chose from the population the distribution for men between the ages of 25 and 54—cp. *Statistisk Årsbok för Stockholms stad* (1953). (The distribution according to social status in the present series is significantly different from the distribution in the general male population in each 5 year age-group (from 25 to 54). Hence, the difference in the age distributions between the fathers of the observed children and the male population may be disregarded). From the present series I excluded the cases that were grouped according to the mother's occupation —i.e. one case in Group I, 9 cases in Group II and 12 in Group III.

The overwhelming majority of the children in the present series were born in 1946. They were thus seven years of age[1].

In a few instances the children were born in 1947. These were children who having passed the maturity test, were permitted to start school before the usual age. In some few instances the children were born in 1945. The schooling of these children had been postponed for one year, as they were not considered mature enough for education in the year of their seventh birthday or possibly were ill at that time.

The series can be expected to furnish a comparatively fair random sample of the corresponding age group among the general population in Stockholm. Mentally defective children with an intelligence quotient of approximately less than 70–75, however, are not included. These children are not admitted to elementary schools. On the other hand, borderline cases are represented. The small group of children attending private schools is also excluded. However, in 1953 merely 756, i.e. 6 per cent out of all 12,495 first-form pupils attended private schools. The group of private-school pupils is thus so small as to be without appreciable importance as a selective factor.

The number of pupils in the forms studied was 2,018, i.e. 17.2 per cent of all 11,739 pupils attending in that year the first forms of the Stockholm elementary schools. A questionnaire was sent to the parents of all these children. In 1,992 instances, i.e. 98.7 per cent, answers were received.

Only 26 questionnaires remained unanswered. In 7 instances it could not be ascertained whether the children had left the respective schools or were still attending. In 19 instances no reply had been received though the children remained at their schools. As stated on the "health card" of the school, two of them had passed urine during sleep. There being a fair agreement in respect of the statements as to enuresis between the questionnaires and the "health cards" (cp. p. 389), it is unlikely that the presence of enuresis was responsible, to any appreciable extent, for the questionnaires remaining unanswered. The children excluded from the survey because no reply was received to the questionnaire sent off, thus probably did not influence the result of the following analysis to any considerable degree.

Consequently, the present series includes 1,992 cases. However, since the information in certain instances is incomplete, the material is somewhat reduced in some of the following computations.

219 children were stated to suffer from enuresis (cp. Table 2). The 1,773 children not presenting enuresis served as a control group in the analyses of school maturity tests and distribution among social groups. In the analyses of other factors studied, in the first place, the 131 enuretics—88 boys and 43 girls—were set apart who at the time of

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[1] In Sweden children usually start school during the calendar year in which their seventh birthday occurs.

investigation had not yet attained bladder control. These were divided into 3 groups, viz. children passing urine only during sleep, children without bladder control both at night and in daytime, and children incontinent only during the day. As the two latter groups consisted of but 8 and 14 cases, they were supplemented, respectively, with those children who had been night-and-day-wetters—27 cases—and those who had been day-wetters only—7 cases—but had attained control of bladder action at the time of investigation. The selected series of enuretics this includes 152 children; 96 cases—72 boys and 24 girls—with nocturnal enuresis only, 35 cases—20 boys and 15 girls—with nocturnal as well as diurnal enuresis, and 21 cases—11 boys and 10 girls—with diurnal enuresis only. A control series was selected from the group of non-enuretic children, in the following manner. A control case was allotted to each enuretic child. The cases were matched pair by pair with regard to sex, form at school, and social group. Within the social group that child was chosen whose age was most close to that of the enuretic child in question. In 11 instances—five belonging to Social Group I, three to Social Group II, and three to Social Group III—there was no non-enuretic case of the same Social Group as the enuretic case in the same form. The child in Social Group II, III and II, respectively, of nearest age was then selected as a control case.

It was considered appropriate to attribute greater importance, in selecting the control cases, to the school form than the social group, viz. for the following reasons.

First, some of the computations carried out are based on the behaviour of the children at school, and partly on observations made by the form master (see p. 385). By matching the children according to the school form, thus a more uniform school environment and in certain respects a more uniform appraisal were obtained. Secondly, in a number of the schools the children are referred to a given form partly on the basis of the result of the school maturity test. This is done either in such a manner that the separate forms correspond to one another in respect of the intelligence level, or so as to ensure that the intelligence level be uniform within each of the forms. When the children are referred to the respective forms by the latter method of selection, a certain stabilization of the material as to intelligence is ensured by matching the cases according to the school form.

The average ages in the groups of enuretics and controls were 7 years and 4.1 months ± 0.4 months and 7 years and 4.2 months ± 0.3 months, respectively. It can be claimed that this series of non-enuretic children is well suited as a control group to the selected group of enuretics for the purpose of the following computations.

Below these two groups are referred to as *the matched material.*

As mentioned above, a questionnaire was sent by me to the parents of those children who were selected for the present investigation. It was distributed and returned in a sealed envelope, under circumstances which ensured discretion. The parents were thus able to answer the questions candidly. The text of the questionnaire is given in the Appendix (p. 401).

Certain difficulties are encountered in formulating such a questionnaire. The heading should impress upon the reader the importance of answering correctly. Furthermore, if the questionnaire contains too many questions, the parents are likely to find it unduly comprehensive and to feel that they are incapable of answering it. On the other hand, it must not be unduly brief if sufficient data are to be obtained. The items should be uncomplicated in the sense of being intelligible to the parents and easily interpretable to the investigator.

If in a given case a question was left unanswered, this case was excluded from the analysis of that special factor. As regards the matched material, both the control and the enuresis case were excluded. If the social data were incomplete they were supplemented by information obtained from the Inland Revenue Office of the City of Stockholm or the parish registers.

In conducting investigations like the present it is naturally desirable that all children are personally examined by the investigator and the parents personally interviewed. In the case of a large series, however, it is very difficult as well as exceedingly tedious and expensive to carry through such examinations. The main purpose of the present study was to arrive at a rough estimate of the morbidity risk of enuresis in the general population for a subsequent clinical and genetic study of enuresis. Therefore, I did not deem it necessary to make a personal examination of the cases. Moreover, the children and their parents were personally explored by the school-physicians during the earlier part of the autumn term and certain social data and results of intelligence tests were available (see p. 385).

The intention was to examine personally the 304 selected matched cases, but this I had to give up for financial reasons. I still considered it possible to make a statistical analysis of certain clinical and social data on the basis of the questionnaire and the examination of the school-physicians, for the following reasons. The data that were analysed are not of a very complicated nature. Moreover, the computations do not aim at providing information as to the absolute frequencies of the separate factors, but only at a comparison between two matched groups that are investigated according to uniform principles. There are no adequate reasons to suspect that the information obtained about the two groups differs in reliability. The parents in the group of enuretics might be supposed to be more truthful seeing that they admitted enuresis in their children, whereas in the group of controls there may be enuretics whose parents, denying enuresis, might also be suspected of negligence in answering the remaining questions. In actual fact, the incidence of observed enuretics according to the questionnaire is even higher than that emerging from the investigations of the school-physicians based on personal interviews with the parents (cp. p. 385). The results of the calculations must, however, be critically interpreted.

As mentioned above, every child was personally examined by the school-physician during the earlier part of the autumn term. The observations made by this physician were entered on a so-called "health card" with which each child was provided when starting school. By courtesy of the Senior Physician of the Stockholm elementary schools the health cards of the children included in the survey were made available to me[1].

The examination by the school-physician consists of a physical routine examination including urine tests for albumin and glucose; where albumin is present, the spun sediment is also examined. In addition the physician asks those responsible for the care of the children for statements as to the mental and physical development and condition. The "health card" also contains information of noteworthy mental reactions observed by the teachers, as well as notes made by the school nurse pertaining to certain social data. To every "health card" is further attached a form filled in by the responsible person as to the state of health of the child and various purely social matters. In those instances where the children had been subjected to special explorations, e.g. psychiatric examination, the findings are given on the "health card". It was possible to trace the "health cards" also in most of the instances, where the children at the time of investigation had moved from Stockholm or for any reason had interrupted their schooling. The very few cases, where this could not be done, were excluded from the computations based upon information derived from the "health card" or forms filled in by the parents. If a case had to be excluded, the corresponding control case or enuresis case was also cancelled.

The details obtained from the "health cards" and used in the assessment of the present material, are as follows:

Weight at birth
Height at the start of the autumn term
Weight at the start of the autumn term
Previous illnesses
Difficulties of bladder control
Occupation of the person responsible for the care of the child
Number of siblings and position in birth series
Size of flat
Number of persons living in the flat

The annotations under the headings:

Urine
Speech difficulties
Nervous system, mental state
Mental disturbance

The following information derived from the form filled in by the parents was used:

Occupations of parents
Birth years of siblings
Deceased siblings
Previous illnesses
Disturbances of sleep

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[1] I am highly indebted to Senior Physician *Urban Hjärne*, M.D. for this courtesy and for facilitating my collection of material.

All data listed above pertain to the conditions existing at the start of the autumn term. In those instances where the social information was incomplete, it was supplemented by consulting the Inland Revenue Office of the City of Stockholm or the parish registers. The cases in which data were lacking or were incomplete and could not be supplemented, were excluded from the assessment of the factor concerned.

Furthermore, the results of the obligatory school maturity tests were studied.

Two different maturity tests, both group tests, were used. In a number of the schools the children had been tested according to an abbreviated version of Wigforss's so-called Kalmar test—*Wigforss* (1946 and 1951). In other schools Lindahl's test—*Lindahl* (1951) had been performed.

STATISTICAL METHODS[1]

To test the hypothesis that a number of samples are taken from a homogeneous population, I used the graphic method described by *Mosteller* & *Tukey* (1946, 1949).

When the number of observations in any of the groups to be compared does not amount to at least ten, I have refrained from making statistical analyses.

Testing the agreement between an observed and a hypothetical distribution (e.g. that found in the population) with two or more degrees of freedom, I used the χ^2 test—cp. for instance *Cramér* (1945).

The standard error of a percentage, $_{\varepsilon}p$, was computed from the formula

$$\varepsilon p = \sqrt{\frac{p\ (100 - p)}{n}}$$

where p is the percentage and n the number of observations.

The standard error of the mean of the differences between paired observations, $_{\varepsilon}\bar{d}$, was obtained with the formula

$$\varepsilon \bar{d} = \frac{\sigma}{\sqrt{n}}$$

where σ is the standard deviation, and n is the number of pairs of observations.

The standard deviation, σ, was calculated from the formula

$$\sigma = \sqrt{\frac{\Sigma\ (d - \bar{d})^2}{n - 1}}$$

where $(d - \bar{d})$ is the deviation of a difference from the mean of the differences, and n is the number of pairs of observations. A difference is considered

significant ** if $0.001 < p \leq 0.01$
significant *** if $p \leq 0.001$

Owing to the relatively high degree of uncertainty inherent in the data I have not considered a difference significant if $0.01 < p$.

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[1] I gratefully acknowledge the valuable co-operation in the statistical analysis of Fil. kand. *Staffan Ekblom* of the Statistical Research Group at the University of Stockholm.

MORBIDITY RISK

Previous Investigations

The statements found in the literature as to morbidity risk and incidence of enuresis in series selected more or less at random vary considerably. Presumably this is chiefly due to the principles of selection and the investigation methods.

Hubert (1933) estimated the incidence of nocturnal enuresis at between 8 and 10 per cent among children from residential schools. However, he gave no account of the material on which he based this figure.

Michaels & Goodman (1938)[1] in a group 437 so-called normal children—about the same number of boys and girls –in the Detroit Recreation Camp, found enuresis after 3 years of age in 24.7 per cent of the cases. At the age of eight, 9.2 per cent of the children were still enuretics and at age of ten, 3.9 per cent.

In a population study from Germany, *Grobig* (1941) found a morbidity risk figure for nocturnal enuresis of 4 out of 100. Unfortunately, he gave no account of his diagnostic criteria.

Gordon (1942) reported on nocturnal enuresis in 14 (7 per cent) out of 200 school children between the ages of 5 and 14 (no account of sex distribution).

Levine (1943) found that the ratio of bed-wetters among all recruits at the Norfolk Naval Training Station was 12 per 1,000.

According to *Thorne* (1944) 16.1 per cent of a group of 1,000 consecutive selectees questioned at an army induction station reported nocturnal enuresis—wetting regularly once or more times weekly—at the age of five, 12.9 per cent at the age of seven, 8.5 per cent at the age of ten and 2.5 per cent at the age of 17.

In an inquiry among 5,000 children between 5 and 10 years of age, in well-ordered, good Residential Homes for Poor-Law Children, *Sheldon* (1944) found an incidence of enuresis of 5 per cent. No detailed description is given of the material.

In *Despert*'s (1944) group of 60 children admitted to the Payne Whitney Nursery School the morbidity risk of enuresis—arbitrarily defined as children who were not trained for day at 2½ years and for night at 3 years—was 23 per cent (10 out of 31 boys and 4 out of 29 girls). The children were stated to be "normal" and coming from families with fairly homogeneous social and cultural backgrounds.

Gedda (1948) found nocturnal enuresis in 32 out of 879 children (3.6 per cent) —436 boys and 443 girls—from Gothenburg who had recently started school. They were all about 7 years of age. At 11 only 3 of the 32 enuretics had ceased to wet —cp. *Gedda* (1953).

According to the Joint Committee of the B.M.A. and Magistrates Association (1948) about 1 in 7 of the total population have at some time suffered from nocturnal enuresis. As enuretics were considered children who wet the bed at night "to a significant degree" after the age of three. The Committee, however, gave no account of the material on which the reported incidence is based.

Hallgren (1950) found that 16 out of 173 (9.2 per cent) consecutive children—77 boys and 96 girls—at a Stockholm secondary school were still bed-wetters at the age of four.

On the basis of the census figures for a small community in northern Norway,

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[1] It is to be regretted that the original paper published in Am. J. Orthopsychiat. *4*: 79, 1934 was not available to me.

Bremer (1951) found an incidence of 12 out of 271 (4.4 per cent)—145 boys and 126 girls—of enuresis in children between the ages of 5 and 14.

In his series of 2,391 elementary school children from Hamburg, selected at random, *v. Harnack* (1953) found that 10.7 per cent of the cases had suffered from involuntary micturition after the age of three. At the age of six to seven, 4.5 per cent were enuretics.

Klackenberg (1955) investigated a series of 315 children—48.6 per cent boys and 51.4 per cent girls—from a children's welfare centre in Stockholm with regard to the age at which they ceased to wet their beds. He regarded the children as night-trained if no wetting had occurred during a continuous period of 2–3 months. When nocturnal enuresis started afresh after a dry interval exceeding 2–3 months, the time of cessation was none the less calculated from the commencement of the first dry period. The author found the incidence of bed-wetting—both sexes taken together—to be 7 per cent at the age of four. The corresponding incidence rates at the ages of three and six were 13 and 4 per cent, respectively. However, though possessing a high degree of reliability, the figures refer to bed-wetting defined in a very restricted way that presumably excludes a not inconsiderable part of the enuretics. Presuming that children wetting continually since infancy represent about 75 per cent of all enuretics (see p. 392), the total morbidity risk for nocturnal enuresis past 4 years of age in Klackenberg's series would be approximately 9 per cent.

The incidence of enuresis in child-psychiatric series is stated to be about 18–27 per cent—*Addis* (1935), *Weigl* (1938), *Schachter & Cotte* (1941), *Kanner* (1948), *Cremieux* (1950). *Bakwin & Bakwin* (1954).

Most authors have found that enuresis is more common among boys —cp. e.g. *Grover* (1918), *Beverly* (1933), *Rauchfuss* (1939), *Stockwell* and *Smith* (1940), *Schachter & Cotte* (1941), *Sheldon* (1944), *Kanner* (1948), *Hodge & Hutchings* (1952), *Turton & Spears* (1953). Other authors—e.g. *Bakwin & Bakwin* (1954)—have found no sex difference in the incidence of enuresis. The different opinions may be largely explained by selective factors.

Addis (1935), reporting on a control series, found 189 boys (60.2 per cent) among 314 children suffering from nocturnal enuresis versus 723 (52.0 per cent) among 1,391 non-enuretic children—both series being taken from the same Child Guidance Clinics in London. The difference is not statistically significant.

Weiss (1936) found 65 per cent males among 187 enuretic children seen at the Philadelphia Child Guidance Clinic versus 68 per cent among 638 children of the general clinic admission for all patients. The correspondence can be deemed satisfactory.

Investigations with unselected materials indicate that there is no sex difference as regards the incidence of enuresis in children.

Gedda (1948), among elementary school children about seven years of age, reported on nocturnal enuresis in 14 out of 436 boys (3 per cent) and in 18 out of 443 girls (4 per cent).

Crosby (1950) found no sex difference in the morbidity risk of enuresis in parents and siblings of 73 enuretic children.

Hallgren (1950), in his series of consecutive secondary-school children, found the morbidity risk figure for nocturnal enuresis—wetting after the fourth year—to be 9 out of 77 (11 per cent) among boys and 7 out of 96 (7 per cent) among girls.

In his population study from Northern Norway, *Bremer* (1951) reported on incidence figures for nocturnal enuresis among boys and girls, between the ages of five and fourteen, of 5 out of 145 (3 per cent) and 7 out of 126 (6 per cent), respectively.

v. Harnack (1953), investigating a series of 2,391 elementary school children —1,243 boys and 1,148 girls—selected at random, found no significant sex difference as to the incidence of involuntary micturition after the age of three, nor of enuresis after the age of six to seven.

The Present Material

The definition of enuresis is given on page 379.

Children wetting only occasionally were not counted as enuretics. For this, wetting at least once a month was required.

As regards 34 children referred to the group of enuretics—in most cases children who ceased to wet before 5 years of age –there is no information about the frequency of wetting. The majority of children have wetted several times a week or more, and all cases except 3 have wetted oftener than once a month. The frequencies refer to that time after the age of four, when the children wet most frequently.

The observed incidence figures for enuresis in the present study are probably minimum rates. The parents, for example, in some case may have concealed an enuresis actually present, being ashamed of admitting it. On the other hand, as regards diurnal enuresis, children involuntarily voiding but small amounts and therefore not strictly referable to the enuresis group, could not be excluded on the basis of the data available.

It is of great interest to compare the information extracted from the questionnaire with that emerging from the school health card (cp. p. 384). Only nocturnal enuresis is regularly entered on the card. The comparison has therefore been limited to bed-wetting. Information in this respect was supplied by the questionnaire in 158 of the 163 cases included in the present material, and by the health card in 136 (in two of the cases the health cards were not available). There is no reason to suspect that a positive statement of enuresis is not reliable. Therefore, it may be stated that the information about nocturnal enuresis obtained from the questionnaire is even better than that emerging from personal interview by the school physician.

As regards the 117 children who were still bed-wetters, the correspondence is better; 114 were found through the questionnaire and 111 through the "health card".

The incidence figures for nocturnal and diurnal enuresis at different ages, found in the present study, will be seen from Table 2 and fig. 1.

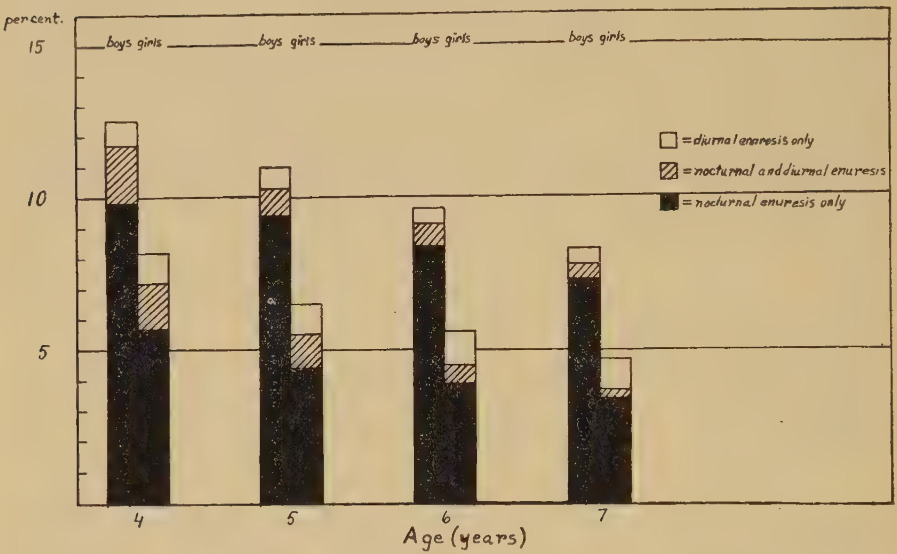

Fig. 1.
Incidence of Nocturnal and Diurnal Enuresis at Different Ages.

Information about the age of cessation was not available in 9 enuretic cases —one with nocturnal enuresis only, one with diurnal only, and 7 with nocturnal as well as diurnal enuresis (in the last group the age of cessation of diurnal enuresis was unknown in all cases and that of nocturnal enuresis in one case)— who wetted after the fourth year, but had ceased to wet at the time of examination. These cases were referred to the age group of 4 years.

The total morbidity risk of enuresis is 13.2 ± 1.0 per cent in the group of boys and 8.4 ± 0.9 per cent in the group of girls. The morbidity risk of nocturnal enuresis is 12.2 ± 1.0 per cent among boys and 7.3 ± 0.9 per cent among girls and that of diurnal enuresis 2.9 ± 0.5 per cent and 2.7 ± 0.5 per cent, respectively.

At the age of seven, the incidence of nocturnal enuresis is 7.8 per cent among boys and 3.7 per cent among girls, and that of diurnal enuresis 1.0 per cent and 1.3 per cent, respectively.

The morbidity risk of nocturnal enuresis is significantly *** higher in the group of boys than in the group of girls. As regards diurnal enuresis there is no sex difference in the morbidity risk.

TABLE 2

Incidence of Nocturnal and Diurnal Enuresis at Different Ages.

Enuresis	Boys		Girls		Total	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
4 Years						
Nocturnal only	105	9.8	53	5.7	158	7.9
Nocturnal and Diurnal	20	1.9	14	1.5	34	1.7
Diurnal only	9	0.8	9	1.0	18	0.9
Total: wetting	134	12.6	76	8.2	210	10.5
Total: dry	933	87.4	849	91.9	1782	89.5
Total	1067	100	925	100	1992	100
5 Years						
Nocturnal only	100	9.4	41	4.4	141	7.1
Nocturnal and Diurnal	10	0.9	10	1.1	20	1.0
Diurnal only	8	0.7	9	1.0	17	0.9
Total: wetting	118	11.1	60	6.5	178	8.9
Total: dry	949	89.0	865	93.5	1814	91.1
Total	1067	100	925	100	1992	100
6 Years						
Nocturnal only	90	8.4	36	3.9	126	6.3
Nocturnal and Diurnal	8	0.7	6	0.6	14	0.7
Diurnal only	5	0.5	10	1.1	15	0.8
Total: wetting	101	9.5	53	5.7	155	7.8
Total: dry	966	90.5	872	94.3	1837	92.2
Total	1067	100	925	100	1992	100
Not Dry						
Nocturnal only	78	7.3	31	3.4	109	5.5
Nocturnal and Diurnal	5	0.5	3	0.3	8	0.4
Diurnal only	5	0.5	9	1.0	14	0.7
Total: wetting	88	8.3	43	4.7	131	6.6
Total: dry	979	91.7	882	95.3	1861	93.4
Total	1067	100	925	100	1992	100
All Enuretics						
Nocturnal only	110	10.3	53	5.7	163	8.2
Nocturnal and Diurnal	20	1.9	15	1.6	35	1.8
Diurnal only	11	1.0	10	1.1	21	1.0
Total: wetting	141	13.2	78	8.4	219	11.0
Total: dry	926	86.8	847	91.6	1773	89.0
Total	1067	100	925	100	1992	100

TYPE OF ENURESIS

Previous Investigations

In most studies enuresis is reported to have existed since infancy in about 75–80 per cent of the cases—cp. e.g. *Anderson* (1930), *Weigl* (1938), *Backus & Mansell* (1944), *Stalker & Band* (1946), *Braithwaite* (1950), *Øster* (1951). There are, however, also series in which this figure is smaller. Thus, *Hubert* (1933), *Campbell* (1934), *Stockwell & Smith* (1940) and *Winsbury-White* (1941) found figures of 41, 65, 58 and 49 per cent, respectively. The varying figures can be explained by selective factors on collecting the materials.

Diurnal enuresis is less frequent than nocturnal enuresis, and is unusual unless combined with night wetting.

In different series of enuretics the incidence figure of cases suffering from diurnal enuresis only varies between one and 7 per cent., and that of cases with diurnal as well as nocturnal enuresis between 10 and 70 per cent: *Anderson* (1930), *Campbell* (1934), *Weigl* (1938), *Stockwell & Smith* (1940), *Schachter & Cotte* (1941), *Winsbury-White* (1941), *Kanner* (1948), *Braithwaite* (1950), *Hodge & Hutchings* (1952), *Bakwin & Bakwin* (1954), and others. The considerable variation in the latter incidence can largely be explained by selective factors.

The Present Material

The data obtained as to whether enuresis had continuously been present from birth onwards or had been preceded by a dry period, are uncertain. Statements as to limited dry periods about one year or more before the age of 4 were received in 19 cases (14 per cent) among the nocturnal and in 6 (11 per cent) among the diurnal enuretics.

Nocturnal enuresis only is observed in 74.4 per cent of the enuretic cases, nocturnal as well as diurnal enuresis in 16.0 per cent, and diurnal only in 9.6 per cent (cp. Table 3). There is no significant difference as to the sex distribution between the three groups of enuretics.

TABLE 3

Incidence of Nocturnal and Diurnal Enuresis in the Group of Enuretics.

Enuresis	Boys		Girls		Total	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Nocturnal only	110	78.0	53	68.0	163	74.4
Nocturnal and Diurnal	20	14.2	15	19.2	35	16.0
Diurnal only	11	7.8	10	12.8	21	9.6
Total	141	100	78	100	219	100

Nocturnal enuresis in most cases of the present series is the predominant symptom in children suffering from nocturnal as well as diurnal enuresis. In 28 of these cases the age of cessation of both nocturnal and diurnal enuresis is known. In 12 the duration was longer for nocturnal enuresis, and in 10 the duration was equal. Moreover, nocturnal enuresis was more frequent in 11 of the 26 cases about whom information was available in this respect, and equally frequent in 9. The number of observations, however, is small.

It is of great interest to know whether the frequency of wetting is of prognostic value with regard to the duration of enuresis—i.e. if the children who wet more often cease to wet at a later age than those who wet less often. The distribution of the children with nocturnal enuresis in the present material as regards frequency of wetting versus age of cessation is seen from Table 4.

Children with a dry period prior to the onset of enuresis were excluded from the table and from the statistical analysis. In the calculations boys and girls were dealt with separately. Because of the relatively small size of the material, cases that had ceased to wet were considered as one group. This group was compared with the group of cases that were not dry. As regards boys, those who wetted once a week or less were treated as one group. The groups of boys wetting several times a week and once a night or more, respectively, were dealt with separately. The number of observed girls being comparatively small, the group of girls wetting once a night or more had to be compared with the cases wetting less than once a week regarded as one group.

The groups of children suffering from nocturnal as well as diurnal enuresis and diurnal enuresis only are too small for a statistical analysis in this respect.

As will be seen from Table 4, the incidence figures for boys who were not dry, in the respective groups of cases wetting once a week or less, several times a week, and every night and more, are 7 out of 20, 25 out of 31, and 24 out of 30, respectively. The difference is statistically significant *** (df = 2). As regards girls, there is no significant difference in the incidence of cases who were not dry between the group of cases wetting every night, 9 out of 16, and that of cases wetting less often, 13 out of 22.

Thus, the analysis has shown that in the present series there is in the group of boys with nocturnal enuresis a positive association between the frequency of wetting and the duration of enuresis. In the group of girls no association of this kind was found. The observed number of girls with nocturnal enuresis, however, is comparatively small.

It will also be seen from Table 4 that there is no statistically significant difference between the groups of boys and girls with nocturnal enuresis as to the frequency of wetting. Nor is there any significant sex difference as to the duration of nocturnal enuresis among children with nocturnal enuresis only.

TABLE 4

Frequency of Wetting Compared with Duration of Nocturnal Enuresis: Cases with a Dry Period Before Start of Enuresis Excluded.

Frequency	Duration														
	4-5 years			5-6 years			6-7 years			Not dry			Total		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Once a month	–	–	–	1	–	1	–	–	–	1	1	2	2	1	3
Twice a month	–	–	–	5	–	5	5	–	5	6	2	8	16	2	18
Once a week	1	2	3	1	–	1	–	–	–	–	1	1	2	3	5
Several times a week	3	2	5	1	2	3	2	3	5	25	9	34	31	16	47
Every day or more	–	1	1	4	4	8	2	2	4	24	9	33	30	16	46
Total	4	5	9	12	6	18	9	5	14	56	22	78	81	38	119

In analysing the frequency of wetting, those children who wetted once a week or less were grouped together. The respective groups of cases wetting several times a week and every night or more, were dealt with separately (df = 2). The number of boys in the three groups is 20, 31 and 30, respectively, and that of girls 6, 16 and 16.

When analysed as to duration of nocturnal enuresis, the material was divided into two groups, viz. children who had ceased to wet, and children who were not dry. The numbers of boys in the respective groups are 25 and 56, and those of girls 16 and 22. The number of observed girls in the groups of cases with nocturnal as well as diurnal enuresis and diurnal enuresis only is too small for a statistical analysis in the above respects.

A calculation was also made to ascertain whether concomitant diurnal enuresis might be of value in gauging the prognosis of nocturnal enuresis. This could not be proved on the basis of the present series of children aged seven. There is no significant difference between the group of cases with nocturnal enuresis only and that of cases with nocturnal as well as diurnal enuresis as to the incidence of boys who were not dry, nor as to the corresponding incidence of girls (cp. Table 5).

TABLE 5

Duration of Nocturnal Enuresis in Cases with and without Concomitant Diurnal Enuresis: Cases with a Dry Period Before Start of Enuresis Excluded.

Enuresis	Dry before 7 years of age			Not dry			Total		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Nocturnal only	25	16	41	56	22	78	81	38	119
Nocturnal and Diurnal	8	4	12	11	9	20	19	13	32
Total	33	20	53	67	31	98	100	51	151

DIURNAL FREQUENCY OF MICTURITION

Previous Investigations

Diurnal frequency of micturition is common in enuretics. This symptom is reported to occur in about 50 to 80 per cent or more of the cases by *Campbell* (1934), *Stockwell & Smith* (1940), *Winsbury-White* (1941), *Backus & Mansell* (1944), *Bakwin & Bakwin* 1954).

The Present Material

Diurnal frequency of micturition is a very common symptom in the present series, even in cases that are not diurnal enuretics. It is observed in 15 out of 84 (18 per cent) of the matched cases with nocturnal enuresis only, 13 out of 33 (39 per cent) of those with nocturnal as well as diurnal enuresis, and in 5 out of the 19 cases with diurnal enuresis only (cp. Table 6).

TABLE 6

Incidence of Diurnal Frequency of Micturition: Matched Material.

Enuresis		Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Frequency	13	2	15	1	1	2
	Others	48	21	69	60	22	82
	Total	61	23	84	61	23	84
Nocturnal and Diurnal	Frequency	6	7	13	—	—	—
	Others	13	7	20	19	14	33
	Total	19	14	33	19	14	33
Diurnal	Frequency	2	3	5	—	—	—
	Others	8	6	14	10	9	19
	Total	10	9	19	10	9	19
Total	Frequency	21	12	33	1	1	2
	Others	69	34	103	89	45	134
	Total	90	46	136	90	46	136

The incidence of diurnal frequency is significantly ** higher in the group of cases with nocturnal enuresis only and significantly *** higher in the group of diurnal enuretics—cases with and without concomitant nocturnal enuresis considered together—than in the respective groups of matched controls.

There is no case with diurnal frequency of micturition in the control group corresponding to the combined group of children with diurnal enuresis. The statistical analysis, however, was performed on the assumption of one positive observation of diurnal frequency.

As will be seen from Table 6, there is no significant sex difference as to the incidence of diurnal frequency of micturition.

These calculations were made in the combined group of diurnal enuretics with and without concomitant nocturnal enuresis, and in the separate group of nocturnal enuretics only.

TABLE 7
Depth of sleep: Matched Material.

Enuresis	Depth of sleep	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Deep sleep	14	4	18	1	1	2
	Light sleep	6	1	7	2	—	2
	Others	49	19	68	66	23	89
	Total	69	24	93	69	24	93
Nocturnal and Diurnal	Deep sleep	3	4	7	—	—	—
	Light sleep	2	—	2	2	1	3
	Others	14	11	25	17	14	31
	Total	19	15	34	19	15	34
Diurnal	Deep sleep	—	—	—	—	—	-
	Light sleep	—	2	2	1	—	1
	Others	11	8	19	10	10	20
	Total	11	10	21	11	10	21
Total	Deep sleep	17	8	25	1	1	2
	Light sleep	8	3	11	5	1	6
	Others	74	38	112	93	47	140
	Total	99	49	148	99	49	148

DEPTH OF SLEEP

Previous Investigations

It is pointed out by several authors that children suffering from nocturnal enuresis often are heavy sleepers. The incidence figures of heavy sleep are reported to be 50 to 75 per cent or more by *Stalker & Band* (1946), *Braithwaite* (1950), *Hodge & Hutchings* (1952) and others. *Ström-Olsen* (1950) found hypersomnia in 25 out of 28 adult patients suffering from severe nocturnal enuresis and obtained good therapeutic results with large doses of amphetamine sulphate. The depth of sleep was not, in the studies mentioned above, measured by objective methods. Moreover, the authors do not report on control series.

Anderson (1930), investigating a group of 77 enuretic children with regard to depth of sleep, classified 51 per cent as deep sleepers. In his group of 50 "normal controls" the corresponding incidence was 52 per cent.

The Present Material

Information about the depth of sleep was obtained from the questionnaire. It represents the subjective evaluation by the children's parents.

As will be seen from Table 7, there is a significantly *** higher incidence of children who were sleeping deeply in the combined group of children with nocturnal enuresis than in the corresponding group of controls. In the group of children with diurnal enuresis and the corresponding control group, there are no observations of deep sleep.

In the present series a positive association between nocturnal enuresis and deep sleep is thus observed. However, since the depth of sleep was not measured by objective methods, the result must be cautiously interpreted. It is possible, for example, that the parents are more apt to notice deep sleep in an enuretic who has to be roused to avoid bed-wetting. On the basis of the present material, no conclusions as to whether there is a causal relationship can be drawn.

ENCOPRESIS

Previous Investigations

Encopresis is reported to occur in a comparatively high incidence—about 10 per cent—among enuretic children—according to *Anderson* (1930), *Hubert* (1933), *Addis* (1936), *Schachter & Cotte* (1941), *Stalker & Band* (1946), *Kanner* (1948), *Øster* (1951).

The present Material

The incidence of encopresis—after 3 years of age—in the matched material of the present series is given in Table 8. There is no significant

TABLE 8

Incidence of Encopresis: Matched Material.

Enuresis		Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Encopresis	5	1	6	2	—	2
	Others	55	20	75	58	21	79
	Total	60	21	81	60	21	81
Nocturnal and Diurnal	Encopresis	7	1	8	1	—	1
	Others	11	14	25	17	15	32
	Total	18	15	33	18	15	33
Diurnal	Encopresis	4	2	6	—	—	—
	Others	6	3	9	10	5	15
	Total	10	5	15	10	5	15
Total	Encopresis	16	4	20	3	—	3
	Others	72	37	109	85	41	126
	Total	88	41	129	88	41	129

difference in this respect between the group of cases with nocturnal enuresis only and the corresponding group of controls. As regards the combined group of cases with diurnal enuresis with and without concomitant nocturnal enuresis, there is a significantly *** higher incidence of encopresis than in the corresponding group of controls.

SUMMARY AND CONCLUSIONS

(1) A study of enuresis with reference to the morbidity risk and symptomatology was made on the basis of a representative series of 1,992 elementary-school children, all of them being about seven years of age. For certain calculations, i.e. of diurnal frequency of micturition, depth of sleep, encopresis, a series of 152 enuretic children was selected and as many non-enuretic control cases, matched pair by pair with regard to sex, form at school, and social group. The investigations were carried out with the aid of a questionnaire that was sent to the childrens' parents and of the "health cards" of the schools. The latter are based partly on the results of the examinations of the children and on interviews with their parents by the school-physicians.

(2) Enuresis is defined as repeated involuntary micturition after the fourth year of life in the absence of gross organic lesions of causal significance.

The total morbidity risk of enuresis in the present series is 13.2 ± 1.0 per cent in the group of boys and 8.4 ± 0.9 per cent in the group of girls. The respective morbidity risk rates for nocturnal enuresis are 12.2 ± 1.0 per cent and 7.3 ± 0.9 per cent, and those for diurnal enuresis 2.9 ± 0.5 per cent and 2.7 ± 0.5 per cent. At the age of seven, 7.8 per cent of the boys and 3.7 per cent of the girls are still bed-wetters, and 1.0 per cent and 1.3 per cent, respectively, are still day-wetters.

The morbidity risk of nocturnal enuresis is significantly higher in the group of boys than in the group of girls. As regards diurnal enuresis, there is no corresponding sex difference.

(3) Nocturnal enuresis only is observed in 74.4 per cent of the enuretic cases, nocturnal as well as diurnal in 16.0 per cent, and diurnal enuresis only in 9.6 per cent. There is no significant difference as to the sex distribution between the three groups of enuresis.

(4) There is, in the present series, as regards boys with nocturnal enuresis a positive association between the frequency of wetting and the duration of enuresis. In the group of girls no association of this kind is found. Nor is there any sex difference as to the frequency of wetting or the duration of enuresis among children with nocturnal enuresis.

(5) No significant difference is noted between the group of cases with nocturnal enuresis only and that of cases with nocturnal as well as diurnal enuresis as regards the duration of bed-wetting. This applies to boys as well as girls.

(6) Diurnal frequency of micturition is a common symptom in the enuretic children of the present series. It is observed in 35 per cent of the cases in the combined group of children with diurnal enuresis, and in 18 per cent in the group of children with nocturnal enuresis only. In both instances the incidence figures are significantly higher than in the respective groups of matched controls. No sex difference is found as to the incidence of diurnal frequency of micturition.

(7) In the present series a significantly higher incidence of deep sleep is observed in the combined group of cases with nocturnal enuresis than in the corresponding group of matched controls. However, it is not possible, on the basis of the present material, to draw any conclusions as to whether there is a causal relationship. No significant difference is emerging between the group of cases with diurnal enuresis only and the corresponding group of controls as regards the incidence of deep sleep.

(8) A significantly higher incidence of encopresis is observed in the combined group of cases with diurnal enuresis than in the corresponding group of matched controls. As regards the group of cases with nocturnal enuresis only versus the corresponding control group, there is no significant difference in respect of the incidence of encopresis.

(9) Hence, it may be concluded that nocturnal enuresis is a fairly common disorder, and that it occurs more frequently among boys than girls; the morbidity risk figures for the average population may be roughly estimated at about 12 and 7 per cent, respectively. Diurnal enuresis is less common, the morbidity risk figure being about 3 per cent in both sexes, and is in the majority of cases combined with nocturnal enuresis. Furthermore, the investigations indicate that there are positive associations between both nocturnal and diurnal enuresis and diurnal frequency of micturition, between nocturnal enuresis and deep sleep, and between diurnal enuresis and encopresis.

For references see *Hallgren, B.:* Acta phychiat. et neurol. *31*: 405–36, 1956.

APPENDIX

English Translation of the Questionnaire[1]

To the Parent or Guardian.

Bed-wetting is a very common occurrence among children and it often causes considerable suffering to them. An investigation is being undertaken at the Caroline Hospital and the Crown Princess Lovisa Children's Hospital which aims at throwing light on the reasons for bed-wetting, so that we may be able to help the children in their trouble.

We ask you to assist us in this by answering the questionnaire below as fully and accurately as possible. When you have completed it, will you please return it at once in the enclosed envelope to the school for the child's teacher? She will forward it to the school nurse, who in turn will deliver it to me.

The information you give will be regarded as *strictly confidential.* No outside person will get to know that your child wets the bed—neither his (or her) school-fellows nor anyone else. Please note that the form is intended to be filled in for *all* children, even for those who do not wet their beds and have never done so.

If there is anything in the form that you find difficult to answer, please phone 27 94 67 for advice (October 20–23, 6–8 P.M.).

Bertil Hallgren
M.D.

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[1] A few items that were not analysed are excluded.

A. Particulars of the child.

Child's name .... Born ....
Address .... Telephone No. ....
School .... Class .... Teacher ....

Weight at birth
Was the child injured in any way at birth (for example by forceps delivery)?
Has the child wetted the bed?
In that case for how long?
Does the child still wet the bed?

If the child wetted the bed after the age of 4, did (s)he do so usually
- every night or more often?
- several times a week?
- once a week?
- several times a month?
- once a month?
- once in a while?

(underline the most appropriate phrase)

Has the child wetted his/her trousers?
In that case for how long?
Does (s)he still wet his/her trousers?

If the child wetted his/her trousers after the age of 4, did (s)he do so usually
- every day or more often?
- several times a week?
- once a week?
- several times a month?
- once a month?
- once in a while?

(underline the most appropriate phrase)

Has the child soiled his/her trousers?
In that case for how long?
Does (s)he still do so?

Did the child soil his/her trousers
- now and then?
- regularly?

(underline the most appropriate phrase)

In your opinion does the child need to make water
- more often than children in general?
- about as often as most other children?
- less often than children in general?

(underline the most appropriate phrase)

In your opinion is the child
- right-handed?
- left-handed?
- impossible to decide which?

(underline the most appropriate phrase)

Before the child reached shool age, did (s)he prefer his/her left hand to his/her right, so that you had to teach him/her to use the right hand?

Has the child
- sucked his/her thumb or fingers? In that case how long?
- bitten his/her nails? In that case how long?
- walked in his/her sleep?

In your opinion is the child more "nervous" than most other children?

In your opinion does the child sleep
- more heavily than children in general?
- about as heavily as most children?
- more lightly than children in general?

(underline the most appropriate phrase)

Has the child had whooping-cough? In that case when?
Was the child examined by a doctor on that occasion?

B. Particulars of family.

Father (name, date of birth, and occupation)

Mother (name, date of birth, and occupation/if the mother works outside the home/)

Brothers and sisters (name, date of birth/including children who were still-born or died in infancy; state also date of death/)

Do the parents live together (if not, state whether the parents are divorced or separated, or whether one of them is dead, and also when the home was broken up)?

Any further information which you think should be given:

Stockholm 1953

....
Parent or guardian

Received November 3rd, 1955

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(PROFESSOR TORSTEN SJÖGREN) AND THE PAEDIATRIC CLINIC, KRONPRINSESSAN LOVISAS BARNSJUKHUS, STOCKHOLM, SWEDEN
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ENURESIS

II. *A Study with Reference to Certain Physical, Mental, and Social Factors Possibly Associated with Enuresis*

By

BERTIL HALLGREN

INTRODUCTION

In the present study enuresis is defined as repeated involuntary micturition after the fourth year of life in the absence of gross organic lesions of causal significance.

Various factors considered to be of aetiological importance for enuresis are described in the literature. These may be divided into four main groups: (1) Physical disorders. (2) Mental disorders. (3) Environmental factors—including faulty training. (4) Heredity. A comprehensive study of the aetiology of enuresis is beyond the scope of the present investigations and not possible on the basis of the available data. The object of the present study is an analysis of a representative series of elementary-school children suffering from nocturnal and/or diurnal enuresis as well as of a control series with regard to certain physical, mental and social factors possibly of importance as causes of enuresis, or otherwise associated with it.

In a preceding issue of this periodical—Hallgren (1956) an account has been given of the present material and of the statistical methods used.

PHYSICAL DISORDERS

Previous Investigations

Physical illnesses, except gross organic defects or diseases of the urinary or central nervous systems or certain systemic diseases such

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The investigations were carried out with the aid of grants from the State Medical Research Council, from Stiftelsen Therese and Johan Anderssons Minne and from Karolinska Institutet.

as diabetes mellitus and diabetes insipidus, are by most authors considered to be of little significance as causes of involuntary micturition. However, according to the definition (see p. 405), involuntary micturition caused by gross organic lesions is not referred to as enuresis.

On the other had some authors—*Campbell* (1934), *Winsbury-White* (1941), *Fisher & Forsythe* (1954) and others—report on a variety of minor abnormalities of the urogenital tract in about half or more of the enuretic cases. It is, however, very doubtful whether these lesions are to any considerable extent of causal significance to enuresis. The authors do not even quote control series giving the incidence rates for the same lesions in non-enuretic cases. In other series organic lesions considered to be responsible for urinary incontinence are reported in about 10 per cent of the cases—cp. for example *Stockwell & Smith* (1940), *Backus & Mansell* (1944), *Nash* (1949). I have found in the literature but few studies on physical illnesses in enuretics with reference to control series.

Anderson (1930) in comparing a group of 148 enuretic children with a group of 50 "normal controls" (see p. 417), found no difference in the development of dentition, walking, or talking. Nor did he find any significant difference as to the incidence of non-spontaneous births, the figures being 13 and 24 per cent, respectively. In the group of enuretic children the author found early nutritional problems in 30 per cent of the cases versus 6 per cent in the group of control children. The difference is statistically significant. However, the social conditions in the two groups were different (see p. 417).

Gordon (1942) reported on a history of "allergy", i.e. migraine, asthma, hay-fever, and eczema, in the child or the family in 85 out of 128 bed-wetters (65 per cent) as compared with 56 out of 200 control cases (28 per cent). The difference is statistically significant. The author, however, gave no account of the method of selecting the cases. In 48 per cent of the enuretic cases the "allergic" manifestation was migraine. In *Gordon*'s material the incidence of bed-wetters in the group of asthmatics, 5 out of 73 (7 per cent), was not higher than in the control group, 14 out of 200 (7 per cent). But the incidence of bed-wetters in the group of children with migraine, 18 out of 58 (31 per cent), was significantly higher than in the control group, 14 out of 200 (7 per cent). Moreover, the incidence of headaches was significantly higher in a group of bed-wetters, 22 out of 50 (44 per cent), than in the control group, 26 out of 200 (13 per cent). The author suggested that enuresis results from the abnormal mental traits of allergics.

The Present Material

Data regarding physical illnesses were obtained from the "health card" of the schools—cp. Hallgren (1956)—which also yielded information about hospitalization if any. Accordingly, the records could be procured in instances where additional data were required.

In no case of the present series an organic lesion was found which was considered to be the direct cause of the wetting.

TABLE 1

Incidence of Significant Physical Disorder before Four Years of Age: Matched Material.

Enuresis	Physical Disorder	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Inguinal hernia	4	—	4	3	—	3
	Valvular disease of the heart	1	—	1	1	—	1
	Pneumonia	1	1	2	4	2	6
	Hilar tuberculosis	—	—	—	1	—	1
	Prolapse of the rectum	1	—	1	—	—	—
	Total: with physical disorder	7	1	8	9	2	11
	Total: others	65	21	86	63	20	83
	Total	72	22	94	72	22	94
Nocturnal and Diurnal	Inguinal hernia	1	—	1	—	—	—
	Pneumonia	4	—	4	—	—	—
	Total: with physical disorder	5	—	5	—	—	—
	Total: others	12	14	26	17	14	31
	Total	17	14	31	17	14	31
Diurnal	Pneumonia	3	—	3	—	—	—
	Ileus	1	—	1	—	—	—
	Total: with physical disorder	4	—	4	—	—	—
	Total: others	7	10	17	11	10	21
	Total	11	10	21	11	10	21
Total	With physical disorder	16	1	17	9	2	11
	Others	84	45	129	91	44	135
	Total	100	46	146	100	46	146

Significant physical disorders—contagious diseases, slight acute illnesses, allergic manifestations, neurological and urinary tract abnormalities not included (the three latter groups are dealt with separately)—before four years of age were found in 17 enuretics and 11 controls (see Table 1). The difference is not statistically significant.

There was information about neurological disorders before four years of age in four cases of the matched material—one belonging to the group of enuretics and three to that of controls. In one control case no data with regard to neurological disorders were available. Thus, there is no higher incidence of apparent neurological disorders in the group of enuretics.

The neurological disorders found were the following. Posttraumatic epilepsy—the enuretic case—, convulsions of unknown aetiology—two controls—and encephalitis following parotitis—one control case. Another three cases—two enuretics and one control case—had head-injuries with no demonstrable residual symptoms.

It has been stressed—cp. *Annell* (1953)—that whooping cough during the first years of life is a comparatively frequent cause of various mental and neurological disorders. The incidence rates for pertussis before two years of age in the different groups of the matched material are given in Table 2. There is no significant difference in this respect between the groups of enuretics and those of controls.

TABLE 2

Incidence of Whooping Cough before Two Years of Age: Matched Material.

Enuresis		Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Whooping cough	7	1	8	7	5	12
	Others	65	23	88	65	19	84
	Total	72	24	96	72	24	96
Nocturnal and Diurnal	Whooping cough	4	1	5	4	1	5
	Others	14	14	28	14	14	28
	Total	18	15	33	18	15	33
Diurnal	Whooping cough	—	3	3	2	4	6
	Others	11	7	18	9	6	15
	Total	11	10	21	11	10	21
Total	Whooping cough	11	5	16	13	10	23
	Others	90	44	134	88	39	127
	Total	101	49	150	101	49	150

The three groups of enuretics and the respective groups of controls are treated separately in the statistical analysis.

Nor is there any significant difference betwen the groups as to the incidence of allergic manifestations (see Table 3). (The allergic manifestations considered, viz. bronchial asthma, eczema, strophulus are separately entered on the "health card").

TABLE 3

Incidence of Allergic Manifestations: Matched Material.

Enuresis	Allergic Manifestation	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Bronchial asthma	1	—	1	4	1	5
	Eczema	6	1	7	4	2	6
	Strophulus	3	1	4	—	2	2
	Total: allergic	8	2	10	7	4	11
	Total: others	62	20	82	63	18	81
	Total	70	22	92	70	22	92
Nocturnal and Diurnal	Bronchial asthma	2	2	4	—	—	—
	Eczema	1	2	3	2	3	5
	Strophulus	—	1	1	1	2	3
	Total: allergic	3	2	5	3	3	6
	Total: others	14	12	26	14	11	25
	Total	17	14	31	17	14	31
Diurnal	Bronchial asthma	—	1	1	—	—	—
	Eczema	—	1	1	—	—	—
	Strophulus	—	1	1	—	—	—
	Total: allergic	—	3	3	—	—	—
	Total: others	11	7	18	11	10	21
	Total	11	10	21	11	10	21
Total	Bronchial asthma	3	3	6	4	1	6
	Eczema	7	4	11	6	5	11
	Strophulus	3	3	6	1	4	5
	Total: allergic	11	7	18	10	7	17
	Total: others	87	39	126	88	39	127
	Total	98	46	144	98	46	144

Because of the small number of positive observations the group of children with nocturnal as well as diurnal enuresis and that of children with diurnal enuresis only, are treated as one group, as are the respective control groups. The incidence of allergic manifestations in the group of cases with nocturnal enuresis only is 10 out of 92, and in the combined group of the other enuretic cases, 8 out of 52. The corresponding incidence rates for the respective control groups are 11 out of 92 and 6 out of 52.

Urinary tract disorders before four years of age –the matched material—were found in one child with nocturnal enuresis only, in one with nocturnal as well as diurnal enuresis, and in one control case.

The respective diagnoses were pyelitis, recurring cystitis, and pyelitis. Data were not available regarding 6 enuretics and 3 controls.

Pathological urine at the school-examination was found in no case. In 5 enuretics and 2 controls there were no accounts of urinalysis. In one boy with nocturnal enuresis only, there was a history of albuminuria, probably of orthostatic origin.

TABLE 4

Distribution of the Material According to Weight at Birth: Matched Material.

Enuresis	Weight at Birth Grammes	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	2,000 and less	—	—	—	—	—	—
	2,001–2,500	4	—	4	1	1	2
	2,501–3,000	5	2	7	4	2	6
	More than 3,000	63	22	85	67	21	88
	Total	72	24	96	72	24	96
Nocturnal and Diurnal	2,000 and less	—	1	1	—	—	—
	2,001–2,500	1	—	1	—	2	2
	2,501–3,000	2	3	3	1	1	2
	More than 3,000	16	11	27	18	12	30
	Total	19	15	34	19	15	34
Diurnal	2,000 and less	—	—	—	—	—	—
	2,001–2,500	—	—	—	—	1	1
	2,501–3,000	1	4	5	—	1	1
	More than 3,000	10	6	16	11	8	19
	Total	11	10	21	11	10	21
Total	2,000 and less	—	1	1	—	—	—
	2,001–2,500	5	—	5	1	4	5
	2,501–3,000	8	9	17	5	4	9
	More than 3,000	89	39	128	96	41	137
	Total	102	49	151	102	49	151

The distribution of the matched material according to weight at birth appears from Table 4. There is no significant difference in this respect between the group of enuretics and that of controls.

Since the number of observed children born prematurely—weight at birth 2,500 Gm. or less—is small, all enuretic children are treated as one group in the statistical analysis, as are also the control cases. The children born prematurely are treated as one group, the groups of children weighing 2,501–3,000 Gm., and more than 3,000 Gm., respectively, are treated separately (df = 2).

The physical constitution of the children is studied by means of the ratio between height and age and between weight and height. The data about these factors were obtained from the "health card" and refer to the time when the children were about seven years of age. In estimating deviating relationships I used diagrams representing the variations in the general Swedish population as adopted by *Karlberg* (1956). As deviating those children were considered in whom the ratios i.e. height/age and weight/height, fell outside the 95 per cent limits ($2\ \sigma$).

The incidence rates for children in whom the ratio between height and age fell outside the $2\ \sigma$ limits are given in Table 5, and the corresponding rates for children as to the relationship between the weight and the height in Table 6. The difference between the combined group of enuretics and that of controls is in no instance statistically significant. However, with regard to the ratio height/age, a comparatively larger number of enuretics showed a deviating relationship, the probability of the difference being due to random variation being less than 0.05.

TABLE 5

Incidence of Deviating Ratio between Height and Age (According to a Swedish Growth Chart): Matched Material.

Enuresis	Height/Age	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Above 2σ limit	4	—	4	—	1	1
	Below 2σ limit	3	—	3	—	—	—
	Within 2σ limit	63	22	85	70	21	91
	Total	70	22	92	70	22	92
Nocturnal and Diurnal	Above 2σ limit	—	—	—	—	—	—
	Below 2σ limit	—	—	—	—	1	1
	Within 2σ limit	18	14	32	18	13	31
	Total	18	14	32	18	14	32
Diurnal	Above 2σ limit	1	—	1	—	—	—
	Below 2σ limit	1	2	3	1	—	1
	Within 2σ limit	8	8	16	9	10	19
	Total	10	10	20	10	10	20
Total	Above 2σ limit	5	—	5	—	1	1
	Below 2σ limit	4	2	6	1	1	2
	Within 2σ limit	89	44	133	97	44	141
	Total	98	46	144	98	46	144

TABLE 6

Incidence of Deviating Ratio between Weight and Height (According to a Swedish Growth Chart): Matched Material.

Enuresis	Weight/Height	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Above 2σ limit	1	—	1	—	1	1
	Below 2σ limit	—	1	1	1	—	1
	Within 2σ limit	69	21	90	69	21	90
	Total	70	22	92	70	22	92
Nocturnal and Diurnal	Above 2σ limit	1	—	1	—	—	—
	Below 2σ limit	—	—	—	—	—	—
	Within 2σ limit	17	14	31	18	14	32
	Total	18	14	32	18	14	32
Diurnal	Above 2σ limit	—	—	—	1	—	1
	Below 2σ limit	—	—	—	—	—	—
	Within 2σ limit	10	10	20	9	10	19
	Total	10	10	20	10	10	20
Total	Above 2σ limit	2	—	2	1	1	2
	Below 2σ limit	—	1	1	1	—	1
	Within 2σ limit	96	45	141	96	45	141
	Total	98	46	144	98	46	144

The number of positive observations is comparatively small. The enuretics and controls, respectively, are therefore treated as one group (df = 2).

INTELLIGENCE

Previous Investigations

There are several studies on the intelligence of enuretic children. They indicate that the intellectual level among these children does not differ to any considerable extent from that among non-enuretic children. On the other hand, enuresis is very common in low-grade mental defectives, who may be incapable of learning vesical control. Investigations in which there is a high incidence of mentally subnormal enuretics are presumably based on selected materials.

Anderson (1930) in his series of enuretic children referred to the Philadelphia Child Guidance Clinic found an average intelligence quotient of 88 for 77 boys and of 95 for 32 girls. Ten children were classed as "subnormal". The author pointed out that the figures include several children with very low I.Q.s, in whom enuresis was a secondary problem to general trainability. Therefore, he considered that the average intellectual level of enuretic children corresponds to that in the general population.

Hubert (1933) compared a group of 50 children referred to the Maudsley Hospital Child Guidance Department for nocturnal enuresis, with a group of 50 children referred to the same department for other reasons, with regard to the intelligence as measured by psychometric investigation. He found in both groups an equal number of children above and below 100. Moreover, the numbers of children at different levels were roughly comparable.

Addis (1935) noted an average I.Q. (test method not stated) of 97 in a series of 225 children with nocturnal enuresis referred to child guidance clinics in London. 21 (9.3 per cent) of the cases had I.Q.s below 75 and 2 (0.9 per cent) below 50, i.e. were to be classed as low-grade defectives. In the average population approximately 8 per cent of the children have an I.Q. below 80; for references cp. e.g. *Hallgren* (1950). The incidence of low-grade deficinency in the general population is found to be 1.0 per cent for men and 0.75 per cent for women—cp. e.g. *Larsson & Sjögren* (1954). There is thus a good agreement between *Addis*'s series of enuretics and the general population in the distribution according to intelligence. It is intersting to note that among 34 children with I.Q.s of 40–50 in *Addis*'s series, 32 were not enuretics. This shows that enuresis is by no means an invariable symptom of mental deficiency, not even on the low-grade deficiency level.

Weiss (1936), comparing a group of 127 enuretic children between four and eighteen years of age from the Philadelphia Child Guidance Clinic with a group of 617 children from the general clinic admitting all patients, was unable to demonstrate any significant difference between the groups as regards the intelligence quotients. In the group of enuretics 45 per cent had an I.Q. of 90–110.

Rauchfuss (1939) in a group of 107 patients with nocturnal enuresis—3–21 years of age—from the Universitäts-Nervenklinik in Leipzig found 55 (51 per cent) to be “mentally subnormal” according to the Binet-Simon scale.

Stockwell & Smith (1940) reported that in their group of 100 enuretic children from a general children's clinic, intelligence rating by school progress disclosed that 70 of the patients were average, 15 above and 15 below average.

Schachter & Cotte (1941) found over 60 per cent “mentally defectives” in a group of 461 enuretic cases of a child-psychiatric clientele.

Bachus & Mansell (1944) reported on 277 unselected cases of nocturnal enuresis consecutively admitted to a military psychiatric hospital. The school history of the group was considered a little above the average and the “work history” quite the average for the personality type.

Thorne (1944) in his study of 369 inmates of a state school for mental defectives found nocturnal enuresis in 84 per cent of a group of 54 “idiots” versus 13 per cent of 164 “imbeciles” and only 4 per cent of 125 “morons”. No relationship was found between enuresis and moderate grades of mental deficiency.

Kanner (1948) reported that in the group of enuretic children from the Johns Hopkins Hospital all degrees of intelligence were represented, quite in harmony with the general I.Q. distribution among the children seen in the clinic.

Hodge & Hutchings (1952) in their series of 131 enuretic children referred to the child guidance clinics of Somerset Country Council found the distribution of intelligence to be similar to that in the general child population. Only two cases (2 per cent) were found to be “mentally defective”.

Wendt (1952) found mental retardation (diagnostic criteria not stated) in 92 out of 190 children with nocturnal enuresis (48 per cent) referred to the Nerven-Kinderpoliklinik in Leipzig. 25 (13 per cent) were labelled “idiots”, “imbeciles”, or serious “debiles”.

The Present Material

In the schools selected for study intellectual maturity test was obligatory for all beginners—see *Hallgren* (1956). However, some of the children included in the present series had not been tested because they were ill at the time when the group-testing was performed, or were absent for other reasons. Moreover, the test records of one school (Hedvig Eleonora School) could not be found. Data pertaining to the results of the maturity test were available in 1,524 out of the 1,992 cases, i.e. 76.5 per cent.

The distribution of the material as regards the results of the school maturity tests is shown in Tables 7 and 8.

TABLE 7

Test Results According to the Wigforss Scale.

Score	Enuretics			Non-enuretics		
	Boys	Girls	Total	Boys	Girls	Total
			Children Born in 1945			
<3	1	—	1	4	4	8
3–3.4	—	—	—	4	1	5
3.5–4.4	2	—	2	5	3	8
4.5–5.4	—	—	—	—	1	1
≥5.5	—	—	—	—	—	—
Total	3	—	3	13	9	22
			Children Born in 1946			
<3	10	12	22	96	64	160
3–3.4	24	7	31	83	69	152
3.5–4.4	33	16	49	211	198	409
4.5–5.4	16	14	30	125	134	259
≥5.5	4	1	5	24	34	58
Total	87	50	137	539	499	1038
			Children Born in 1947			
<3	—	—	—	—	—	—
3–3.4	—	1	1	1	—	1
3.5–4.4	1	—	1	4	9	13
4.5–5.4	2	1	3	3	6	9
≥5.5	—	—	—	1	—	1
Total	3	2	5	9	15	24

TABLE 8.

Test Results According to the Lindahl Scale.

Score	Enuretics			Non-enuretics		
	Boys	Girls	Total	Boys	Girls	Total
			Children Born in 1945			
<30	—	—	—	1	1	2
30–39	—	—	—	1	—	1
40–49	—	—	—	1	3	4
50–59	—	—	—	1	1	2
≥60	—	—	—	—	—	—
Total	—	—	—	4	5	9
			Children Born in 1946			
<30	3	3	6	8	13	21
30–39	6	4	10	30	26	56
40–49	1	5	6	51	54	105
50–59	4	1	5	30	32	62
≥60	—	—	—	2	2	4
Total	14	13	27	121	127	248
			Children Born in 1947			
<30	—	—	—	1	—	1
30–39	—	—	—	1	—	1
40–49	1	—	1	1	3	4
50–59	—	1	1	2	1	3
≥60	—	—	—	—	—	—
Total	1	1	2	5	4	9

The separate score groups in the tables correspond, in accordance with a standard system, to the marks, *underkänd*, *B*, *Ba*, *AB*, *a-A*, respectively ("*underkänd*" means unsatisfactory, and "*a-A*" are the highest marks). Of the children tested with the Wigforss method 25 were born in 1945, and 29 in 1947. The corresponding figures for those tested with the Lindahl method were 9 and 11, respectively. The number of children tested in these age groups is too small to allow of statistical evaluation. The analysis in respect of the test results was therefore confined to the children born in 1946.

In the statistical analysis boys and girls were dealt with separately. Owing to the comparatively small number of enuretic children tested with the Lindahl method, the two lowest score groups were arranged in a single group and compared with the two highest score groups also arranged in one group (df = 1). As regards the Wigforss scale, the different score groups are treated separately (df = 4).

There is no significant difference in the distribution as regards the test-results between the group of enuretics and that of non-enuretics.

This applies to both scales and to boys as well as girls. In the group of boys tested according to the Lindahl scale there is, however, a relatively higher number of enuretics than of non-enuretics in the lower score group, the probability of the difference being due to random variation being less than 0.05.

TABLE 9

Mean of Differences in the Test Results between Matched Pairs of Enuretics and Controls.

Enuresis	Test Method	Number of Observations	Mean of Differences $\bar{d}$
Nocturnal	Wigforss	50	0.02 ± 0.15
	Lindahl	14	—5.00 ± 3.18
Nocturnal and Diurnal	Wigforss	21	0.07 ± 0.28
Diurnal	Wigforss	11	—0.37 ± 0.40

The mean of the differences in the test results between the matched pairs of enuretics and controls was also computed. As appears from Table 9, there is in no instance a significant difference in this respect. It must, however, be borne in mind that the children are matched with regard to form at school. If the children were referred to a given form on account of the results of the maturity test, children with similar test results being allotted to the same form—see *Hallgren* (1956)—, this factor may have exercised a levelling influence in the computations alluded to above.

In the statistical analysis the three different groups of enuretics are treated separately. The number of observed children tested according to the Lindahl scale is too small for a statistical analysis in the group of cases with nocturnal as well as diurnal enuresis, and in that of cases with diurnal enuresis only.

NERVOUS DISORDERS

Previous Investigations

Several authors report a high incidence of emotional disturbances and nervous symptoms in enuretic children. It is, however, a moot point to what extent the mental disorders are the direct cause of enuresis.

According to *Krabbe* (1947), *Crosby* (1950), *Braithwaite* (1950), *Poulton & Hinden* (1953), *Bakwin & Bakwin* (1954) and others, mental factors seldom play a dominant part as the primary cause of enuresis. Other authors —*Anderson* (1930), *Gerard* (1939), *Rauchfuss* (1939), *Stockwell & Smith* (1940), *Kanner* (1948), *Hodge & Hutchings* (1952) and others—however, emphasize the aetiological importance of these factors.

Some authors—*Beverly* (1933), *Weiss* (1936), *Michaels & Goodman* (1938 and 1939), *Gerard* (1939), *Huschka* (1943), *Levine* (1943) —consider that enuresis is but one manifestation of a general disturbance of behaviour.

The personality of the enuretic individual is often described as sensitive, timid, dependent, immature and emotionally unstable—*Anderson* (1930), *Beverly* (1933), *Stockwell & Smith* (1940), *Levine* (1943), *Backus & Mansell* (1944), *Kanner* (1948)—but also other personality types are described.

Schachter & Cotte (1950) made a Rorschach analysis of 70 enuretic children and 40 non-enuretic children presenting child-psychiatric problems. There was no appreciable difference in results between the two groups. The authors, however, pointed out that children with enuresis suffer from very much the same mental abnormalities as the children in the group of non-enuretics.

In relatively few studies on mental disorders in enuretics, control groups comparable to the groups of enuretics have been used. Conclusions based on investigations in which there are no control series, must naturally be drawn with caution. Most studies on the subject refer to child-phychiatric series, in which *a priori* a high incidence of mental disorders is to be expected. However, also from series selected at random a connexion between enuresis and mental disorders has emerged.

Below only studies including control series are taken into consideration.

Anderson (1930) studied a child-psychiatric clientele comprising a series of 148 enuretic children (108 boys and 40 girls). As controls he used a group of 12 children (6 boys and 6 girls) without enuresis, but presenting "clearcut neuropsychiatric diagnoses" studied at an orthopaedic out-patient clinic ("organic controls") and a series of 50 "normal" children (25 boys and 25 girls) of "high type and educated families" ("normal controls"). The average ages in the groups were 8–9 years, 8–9 years, and 5–6 years, respectively. The control groups also included children who had suffered from enuresis up to the age of approximately 10 years, but had ceased to wet at the time of investigation. It is evident from the composition of the author's groups that these are not directly comparable as to mental factors. *Anderson* reported a high incidence of emotional disturbances in the group of enuretics. 76 out of 90 children (83 per cent) were classed as infantile, 86 out of 109 (79 per cent) as sensitive, 66 out of 100 (66 per cent) as timid or fearful, and 45 out of 76 (60 per cent) as aggressive. The corresponding ratios in the group of "organic controls" were 4/12, 6/12, 4/12, and 7/12, respectively. As regards the item "infantile", the incidence rate was significantly higher in the group of ennuretics. As to the other items, there was in no instance a significant difference between the two groups. Concerning the group of "normal controls" no corresponding incidence rates were reported. The incidence of thumb-sucking in the group of enuretics was 15 out of 42 (36 per cent) versus 16 out of 50 (32 per cent) in the group of "normal controls". The difference is not statistically significant.

Michaels & Goodman (1935) in a group of 468 so-called normal children at the Detroit Recreation Camp observed a statistically significant positive association between enuresis on the one hand and nail-biting and impediments in speech, respectively, on the other. Moreover, the relative number of enuretics was larger in the group of children with nail-biting and in that of children with temper tantrums than in the respective groups of children without these nervous symptoms ($0.01 < p < 0.05$). No association was observed between "sleep disturbances" and dreaming, respectively, and enuresis. *Michaels & Goodman* considered that enuresis is an important indicator of an ill-balanced personality. The authors found no significant difference between the group of 437 so-called normal children and a group of 224 psychotic persons observed at the Boston Psychopathic Hospital as to the incidence of enuresis, the rates being 24.7 and 17.9 per cent, respectively. On the other hand, they noted (1939) a significantly higher incidence in the group of "psychopathic personalities" and patients with behaviour problems, viz. 61 out of 178 (34.2 per cent). Furthermore, the persistence of enuresis after the age of ten was significantly more frequent in the group of psychotic patients as well as in the "psychopathic" and behaviour-problem group than in the group of "normals".

Weigl (1938) within a series of 800 "nervous" children compared a group of 215 children suffering from enuresis with a group of 585 children not suffering from enuresis with regard to "nervous symptoms". It should be pointed out, however, that the latter group also included children who were enuretics before the time of examination. Both groups consisted of children up to the age of 21 years and referred to the Bukarest Child Guidance Clinic. Anxiety was the only symptom that was found to be positively associated with enuresis.

Levine (1943) found that approximately 24 per cent of all recruits at the Norfolk Naval Training Station receiving discharges for psychiatric conditions were bed-wetters as compared with 1.2 per cent among all recruits at the station.

Ekblad (1948)[1] found nocturnal enuresis in 12 cases (3.1 per cent) in a series of 390 naval conscripts who completed their training without a break and without being sentenced. In a group of naval conscripts who were sent to a psychiatrist or sentenced during their military training, the corresponding incidence was 36 out of 385 (9.4 per cent). The difference as to the incidence of enuresis in the two groups is statistically significant. The author regarded all subjects as enuretics who on being questioned reported bed-wetting for so long a period in childhood that they themselves were able to remember the fact.

Brock (1952) compared two groups of children suffering from nocturnal enuresis, each group including 50 cases. In one group the patients received psychotherapy, in the other they did not. The incidence rates of cured cases in the two groups were 52 and 6 per cent respectively. The difference is statistically significant. However, the average age was somewhat higher in the former group.

In his series of 2,391 elementary school children aged six to seven and selected at random, *v. Harnack* (1953) found a significantly higher incidence of tics in the group of enuretic children than in the other group. He also observed a significant difference as to the incidence of enuresis in the group of children with temper tantrums (“*patologische Wutreaktionen*”) versus that of other children, the incidence rate being higher in the former group. Furthermore, the combined incidence of behaviour disturbances and nervous signs was significantly higher in the group of enuretics than in the group of non-enuretics.

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[1] Personal communication.

The Present Material

The appraisal of the children’s mental condition was based partly on the answers elicited by the questionnaire, and partly on statements as to “nervous” trouble entered on the school “health card”—see *Hallgren* (1956).In the first instance behaviour refers to the conditions at home, and in the second largely to conditions at school. For this reason the pieces of information about the mental condition obtained from the questionnaire and from the “health card”, respectively, are treated separately.

It is obvious that the methods of examination used in the present study do not permit a closer analysis of the children’s mental condition, and that mental factors of significance in connection with the enuresis must have been overlooked.

TABLE 10

Incidence of “Nervous” Behaviour According to the Questionnaire: Matched Material.

Enuresis	Mental Condition	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Nervous behaviour	18	5	23	10	1	11
	Others	44	19	63	52	23	75
	Total	62	24	86	62	24	86
Nocturnal and Diurnal	Nervous behaviour	5	1	6	2	1	3
	Others	13	13	26	16	13	29
	Total	18	14	32	18	14	32
Diurnal	Nervous behaviour	4	3	7	—	—	—
	Others	4	7	11	8	10	18
	Total	8	10	18	8	10	18
Total	Nervous behaviour	27	9	36	12	2	14
	Others	61	39	100	76	46	122
	Total	88	48	136	88	48	136

As appears from Table 10, the incidence of "nervous" behaviour according to the questionnaire is significantly ** higher in the combined group of diurnal enuretics with and without concomitant nocturnal enuresis than in the corresponding group of controls—the matched material. In the group of children with nocturnal enuresis only, as compared with the corresponding control group, no difference in this respect was found. However, also in this instance the relative number of positive observations is larger in the group of enuretics, the probability of the difference being due to random variation being less than 0.05.

The number of positive observations in the control groups to the group of children with nocturnal as well as diurnal enuresis and to that of diurnal enuretics only is comparatively small. Therefore, in the statistical analysis, these groups of controls are treated as one group as are the corresponding groups of enuretics.

The incidence of "nervous" behaviour according to the "health card" is given in Table 11. There is in no instance a significant difference in this respect between the groups of enuretics and those of controls.

TABLE 11

Incidence of "Nervous" Behaviour According to the "Health Card": Matched Material.

Enuresis	Mental Condition	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Nervous behaviour	18	2	20	11	2	13
	Others	53	22	75	60	22	82
	Total	71	24	95	71	24	95
Nocturnal and Diurnal	Nervous behaviour	5	1	6	3	2	5
	Others	15	13	28	17	12	29
	Total	20	14	34	20	14	34
Diurnal	Nervous behaviour	5	3	8	6	—	6
	Others	6	7	13	5	10	15
	Total	11	10	21	11	10	21
Total	Nervous behaviour	28	6	34	20	4	24
	Others	74	42	116	82	44	126
	Total	102	48	150	102	48	150

TABLE 12

Incidence of Nervous Symptoms: Matched Material.

Enuresis	Nervous Symptom	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Thumb-sucking	11	3	14	9	5	14
	Nail-biting	4	3	7	3	1	4
	Total: with nervous symptom	14	5	19	11	6	17
	Total: others	32	13	45	35	12	47
	Total	46	18	64	46	18	64
Nocturnal and Diurnal	Thumb-sucking	3	2	5	3	1	4
	Nail-biting	—	2	2	1	1	2
	Total: with nervous symptom	3	3	6	3	2	5
	Total: others	6	6	12	6	7	13
	Total	9	9	18	9	9	18
Diurnal	Thumb-sucking	1	5	6	—	1	1
	Nail-biting	1	2	3	1	1	2
	Total: with nervous symptom	2	6	8	1	2	3
	Total: others	3	4	7	4	8	12
	Total	5	10	15	5	10	15
Total	Thumb-sucking	15	10	25	12	7	19
	Nail-biting	5	7	12	5	3	8
	Total: with nervous symptom	19	14	33	15	10	25
	Total: others	41	23	64	45	27	72
	Total	60	37	97	60	37	97

In the calculations the three groups of enuretics are treated separately, as are the respective groups of controls.

The occurrence of certain nervous symptoms, i.e. finger-sucking (after the age of five) and nail-biting, is recorded on the questionnaire and the "health card", respectively (see Table 12). There is in no instance a significant difference between the groups of enuretics and the respective groups of controls in the matched material as to the incidence of these symptoms. There is, however, information in this respect in only 64 per cent of the cases. This fact detracts from the reliability of the calculations.

TABLE 13

Incidence of Sleep Disturbances: Matched Material.

Enuresis	Sleep	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Sleep disturbance	12	3	15	6	1	7
	Others	60	21	81	66	23	89
	Total	72	24	96	72	24	96
Nocturnal and Diurnal	Sleep disturbance	4	3	7	1	3	4
	Others	16	11	27	19	11	30
	Total	20	14	34	20	14	34
Diurnal	Sleep disturbance	2	3	5	1	—	1
	Others	9	7	16	10	10	20
	Total	11	10	21	11	10	21
Total	Sleep disturbance	18	9	27	8	4	12
	Others	85	39	124	95	44	139
	Total	103	48	151	103	48	151

The incidence of sleep disturbances according to the "health card", i.e. difficulty in falling asleep and uneasy sleep, appears from Table 13. There is no significant difference in this respect between the groups of enuretics and the respective groups of controls. However, the relative number of sleep disturbances is larger in the combined group of cases with nocturnal enuresis than in the corresponding group of controls. The probability of the difference being due to random variation is less than 0.05.

Since the number of positive observations is relatively small, the cases with nocturnal enuresis only and those with nocturnal as well as diurnal enuresis are treated as one group in the statistical analysis. There is rather more reason to suspect that a connexion exists between nocturnal enuresis and sleep disturbances than between diurnal enuresis and sleep disturbances. The groups of cases with and without nocturnal enuresis, respectively, are therefore treated separately.

Information about somnambulism is obtained from the questionnaire. There is no significant difference between the combined group of all enuretics and the corresponding group of controls as to the incidence of this symptom, the incidence rates being 4 out of 143 and 2 out of 143, respectively.

TABLE 14

Incidence of Speech Disorders: Matched Material.

Enuresis	Speech	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Speech disorder	7	1	8	3	—	3
	Others	63	21	84	67	22	89
	Total	70	22	92	70	22	92
Nocturnal and Diurnal	Speech disorder	3	1	4	—	—	—
	Others	15	13	28	18	14	32
	Total	18	14	32	18	14	32
Diurnal	Speech disorder	4	3	7	2	—	2
	Others	7	7	14	9	10	19
	Total	11	10	21	11	10	21
Total	Speech disorder	14	5	19	5	—	5
	Others	85	41	126	94	46	140
	Total	99	46	145	99	46	145

Since the number of positive observations is small, the 3 groups of enuretics are treated as one group, as are the corresponding groups of controls.

Depth of sleep is considered, in the literature, to have a special connexion with enuresis. This item is therefore discussed separately—see *Hallgren* (1956).

It is generally considered in the literature that there is a positive relationship between speech disorders and mental condition. The incidence of speech disorders, i.e. stuttering, lisping, retarded speech development, indistinct articulation, according to the "health card" is given in Table 14. The incidence observed is significantly ** higher in the combined group of children with diurnal enuresis than in the corresponding group of controls. As regards the group of children with nocturnal enuresis only versus the corresponding control group, there is no significant difference in this respect.

The number of positive observations is comparatively small in the groups of controls to the respective groups of diurnal enuretics with and without concomitant nocturnal enuresis. Therefore, these groups are treated as one group in the statistical analysis.

To sum up the following conclusions may be drawn. According to the information obtained from the children's parents there is, in the matched material of the present series, a significantly** higher incidence of "nervous" behaviour in the combined group of children with diurnal enuresis than in the corresponding group of controls. Furthermore, the observed incidence of speech disorders in the combined group of diurnal enuretics is significantly ** higher than in the corresponding group of controls.

As regards the group of cases with nocturnal enuresis only as compared with the corresponding group of controls, no significant differences in the above respects emerged.

The results indicate that there is a positive association between diurnal enuresis and mental disturbances. It is not, however, possible, on the basis of the present material to draw any conclusions about a possible causal relationship.

LEFT-HANDEDNESS

Previous Investigations.

Anderson (1930) in his study of 148 enuretic children referred to child guidance clinics found 87 per cent to be right-handed and 13 per cent to be left-handed. In the group of 12 "organic controls" (cp. p. 417) all were right-handed. In the group of 50 "normal controls" 68 per cent were right-handed, 8 per cent left-handed, and 24 per cent were reported as primarily ambidextrous.

Michaels & Goodman (1935) found no significant difference in the incidence of enuresis between a group of 416 right-handed children and a group of 52 left-handed children, the incidence rates being 15 and 26 per cent respectively. Both groups consisted of so-called normal children at a camp. As left-handed were also considered those children who, originally left-handed changed to right-handedness and those who were to be considered clearly ambidextrous. Nor did the authors find any significant difference in the incidence of left-handedness between the group of enuretics and that of non-enuretics.

The Present Material.

Data regarding handedness were obtained from the questionnaire. To the group of left-handed were referred those children who were stated to be left-handed, those who preferred the left hand before school age and had been forced to use the right, and those where the parents felt unable to arrive at a decision. As appears from Table 15, there is no significant difference between the groups of enuretics and the respective groups of controls as to the incidence of left-handedness.

ENVIRONMENTAL FACTORS

Previous investigations.

Our knowledge regarding the significance of bladder training for enuresis is still incomplete. Some authors, e.g. *Wooley* (1926), *Anderson* (1930), *Mowrer & Mowrer* (1938), *Gill* (1940), and *Despert*

TABLE 15

Incidence of Left-handedness: Matched Material.

Enuresis	Handedness	Enuretics			Controls		
		Boys	Girls	Total	Boys	Girls	Total
Nocturnal	Left-handed	6	3	9	9	4	13
	Right-handed	66	21	87	63	20	83
	Total	72	24	96	72	24	96
Nocturnal and Diurnal	Left-handed	3	2	5	1	1	2
	Right-handed	17	13	30	19	14	33
	Total	20	15	35	20	15	35
Diurnal	Left-handed	1	1	2	—	1	1
	Right-handed	10	9	19	11	9	20
	Total	11	10	21	11	10	21
Total	Left-handed	10	6	16	10	6	16
	Right-handed	93	43	136	93	43	136
	Total	103	49	152	103	49	152

(1944), consider that faulty training is of importance as a cause of enuresis. On the other hand, *Bakwin & Bakwin* (1954) hold that inadequate training procedures do not in themselves lead to enuresis in any considerable proportion of cases. Rather, in their opinion, intensive training serves to prevent enuresis in a certain number of susceptibles. However, the authors mentioned do not base their conclusions on representativ series of enuretics and controls of which they give accounts. It was not possible, in the present series, to collect information sufficient for a statistical analysis of the factor "training". This factor, however, may be operative in some of the following calculations, i.e. the parents' socio-economic status, size of family, and position in the birth series.

Enuresis is considered to be more frequent in the lower social strata –cp. e.g. *v. Harnack* (1953) and *Bakwin & Bakwin* (1954). There are, however, few statistical studies with reference to environmental factors based on representative series of enuretics and controls.

Addis (1935) compared a group of 314 children suffering from nocturnal enuresis with a group of 1,391 non-enuretic children, both series being derived from the same child guidance clinics in London. The average size of family for enuretics was 3.61 and that for non-enuretics 3.27. There was no significant difference between the groups as regards position in the birth series or position as only child. 44 enuretics (15.7 per cent) and 259 non-enuretics (20.5 per cent) were only children. In a careful study of 30 children suffering from nocturnal enuresis and with I.Q. above 100, *Addis* (1936) found that 14 cases come from "slum houses" and 16 from artisan or superior homes. Of the former 7 recovered and of the latter 5. The author concluded that "enuresis is not merely the product of slum conditions, nor is it less likely to clear up in a poor home than in one with more material comforts." Of the 17 cases with "good" training 6 recovered. The "bad" group —including over-severe training as well as neglect—showed 6 out of 13 recoveries. Thus, no difference in this respect was found.

Weiss (1936) compared a group of 187 enuretic patients at the Philadelphia Child Guidance Clinic with a group of 638 patients of the general clinic admitting all patients with regard to economic status, marital status and size of families. As regards the distribution according to the number of siblings, there was no significant difference between the groups. In the group of enuretics the incidence of broken homes was significantly lower than in the group of controls. There was also a significant difference between the groups in the distribution according to economic status, an over-representation of families living under poor economic conditions, existing in the group of enuretics.

Weigl (1938) found a higher incidence of unfavourable environmental factors in a group of children suffering from enuresis than in a group of children not suffering from enuresis. In the latter group were included cases who were enuretics before the time of examination. Both groups consisted of 200 nervous children referred to the Bukarest Child Guidance Clinic. No significant difference was found between the groups as regards the patient's position in the birth series nor as regards the incidence of broken homes.

Gedda (1948) in his series of 879 elementary-school children found no difference in the incidence of nocturnal enuresis between the group of children to "white-collar workers" and that of others, the rate being 4 per cent in either instance. In the groups of only children, isolated children, i.e. the first or last child if the interval from the child nearest in age was more than 3 years, and others, the respective incidence of enuresis was 3 out of 163 (2 per cent), 13 out of 228 (6 per cent) and 16 out of 488 (4 per cent). The difference between the groups as to the distribution of the enuretics is not statistically significant (df = 2).

v. Harnack (1953), investigating a series of 2,391 elementary-school children, selected at random, found a significantly higher incidence of enuresis among children belonging to the lower social strata than among other children. On the other hand, he did not find any significant difference as to the incidence of enuresis in the group of children with objectively assessable, unfavourable environmental influences versus that of children without such influences.

The Present Material.

It was not possible on the basis of the available data to make a closer analysis of the children's environment. The analysis had to be confined to certain assessable social data.

Social Status.

The classification of the material as regards the social groups is described in a preceding issue of this periodical—*Hallgren* (1956). There is in the present series a significant ** difference between the combined group of enuretics and that of non-enuretics as to the distribution according to social group (cp. Table 16). In the group of enuretics, an under-representation exists of cases belonging to Social Group I—including the so-called upper classes—and an over-representation of cases belonging to Social Group III—including the working classes.

TABLE 16

Distribution According to Social Group: All Cases.

Enuresis	Social Group I	Social Group II	Social Group III	Total
Nocturnal only	20	63	80	163
Nocturnal and Diurnal	2	14	19	35
Diurnal only	3	6	12	21
Total: enuretics	25	83	111	219
Total: non-enuretics	350	659	764	1,773
Total	375	742	875	1,992

The result indicates that enuresis is more common in the lower social strata. Though the possibility of parents in Social Group III being more inclined towards admitting enuresis in their children than other parents, cannot be ruled out, there is little to support such an interpretation.

There is no significant difference as to the distribution according to social group between the three groups of enuretics (see Table 16).

Space in Homes.

The estimation of the available space in the dwellings was made according to the principles adopted by *Enell* (1955). Thus the families of four or more persons per room—kitchen excluded—have been designated as "over-crowded", three persons per room "crowded", and less than three persons per room as families with "good space". It was not possible on the basis of the available data to take into consideration the qualitative standard of the flats.

It appears from Table 17 that there is no significant difference between the group of enuretics and that of controls—the matched material—as regards space in homes.

In the statistical analysis the three groups of enuretics are treated as one unit and compared with the corresponding group of controls (df = 2).

TABLE 17

Available Space in Homes: Matched Material.

Enuresis	Space in Homes	Enuretics	Controls
Nocturnal	Good space	85	84
	Crowded	6	9
	Over-crowded	5	3
	Total	96	96
Nocturnal and Diurnal	Good space	31	32
	Crowded	2	2
	Over-crowded	2	1
	Total	35	35
Diurnal	Good space	18	20
	Crowded	1	1
	Over-crowded	2	—
	Total	21	21
Total	Good space	134	136
	Crowded	9	12
	Over-crowded	9	4
	Total	152	152

Broken Homes.

In the present study broken homes denote homes where the parents were divorced, one of the parents was dead, or the child born out of wedlock and not brought up by both parents. Only those homes were taken into consideration which were broken before the child was 4 years of age or before the start of enuresis.

There is no significant difference as to the incidence of broken homes between the combined group of enuretics in the matched material and the corresponding group of controls (cp. Table 18). However, in two cases with nocturnal enuresis the wetting started in connection with the divorce of the parents.

Size of Family.

As appears from Table 19, there is no significant difference between the groups of enuretics and those of controls—the matched material—as to the number of families of different sizes.

Here, as in the subsequent computations, siblings as well as half-siblings sharing the domicile with the primary case were included. In the statistical analysis the

TABLE 18

Incidence of Broken Homes Before Four Years of Age or Before Start of Enuresis: Matched Material.

Enuresis	Marital Status	Enuretics	Controls
Nocturnal	Parents divorced	11	6
	Born out of wedlock ...	1	2
	Adopted child	—	—
	One parent dead	—	2
	Total: broken home	12	10
	Total: others	84	86
	Total	96	96
Nocturnal and Diurnal	Parents divorced	2	2
	Born out of wedlock ...	—	—
	Adopted child	1	—
	One parent dead	1	—
	Total: broken home	4	2
	Total: others	30	32
	Total	34	34
Diurnal	Parents divorced	2	—
	Born out of wedlock ...	1	1
	Adopted child	—	—
	One parent dead	—	—
	Total: broken home	3	1
	Total: others	18	20
	Total	21	21
Total	Parents divorced	15	8
	Born out of wedlock ...	2	3
	Adopted child	1	—
	One parent dead	1	2
	Total: broken home	19	13
	Total: others	132	138
	Total	151	151

three groups of enuretics and the respective groups of controls are treated separately. The number of observed families of certain sizes is comparatively small. Therefore, as regards the group of "nocturnal enuresis", families with 6 children and more are treated as one unit (df = 5), as regards the group "nocturnal and diurnal enuresis" families with one–two children and 4 children and more, respectively, (df = 2), and as regards the group "diurnal enuresis" families with 3 children and more (df = 2).

TABLE 19

Size of Family and Position in Birth Series: Matched Material.

Enuresis	Enuretics					Controls				
	Number of families	Number of children	Position in birth series			Number of families	Number of children	Position in birth series		
			Oldest	Inter-mediate	Youngest			Oldest	Inter-mediate	Youngest
Nocturnal	8	1				14	1			
	43	2	28	—	15	45	2	18	—	27
	24	3	7	7	10	18	3	5	5	8
	11	4	—	7	4	11	4	2	7	2
	5	5	—	2	3	5	5	1	3	1
	5	6 and more	—	3	2	3	6 and more	—	3	—
Nocturnal and Diurnal	15	1–2	8*	—	6*	23	1–2	13*	—	3*
	14	3	4	7	3	6	3	—	5	1
	6	4 and more	—	6	—	6	4 and more	1	2	3
	6	1				3	1			
	10	2	6	—	4	7	2	3	—	4
	5	3 and more	1	4	—	11	3 and more	1	5	5

* Only children excluded.

Position in the Birth Series.

There is no significant difference between the groups of enuretics in the matched material and those of controls as to the position of the cases in the birth series (cp. Table 19).

In the statistical analysis the material was divided into oldest children, intermediate children, and youngest children. Only children were excluded from the calculations as they furnish no information. The three groups of enuretics are treated separately.

Accordingly, in this manner it was not possible to demonstrate statistically that the birth of a younger sibling is a factor which provokes enuresis. However, in four enuretic cases—three nocturnal and one diurnal—the wetting started in connection with the birth of a sibling. To analyse this factor more closely the age interval was computed between the enuretic case and the control case, respectively, and the succeeding younger sibling (see Table 20). The statistical calculation shows that there is no significant difference, as regards the age interval to the succeeding younger sibling, between the group of enuretics and the control group.

In the statistical analysis, owing to the small number of observed siblings born less than one year after the primary case, the groups of "less than one year" and "1–2 years" are treated as one group (df = 3). Since the number of observations is comparatively small, the three groups of enuretics are treated as one unit as are the corresponding groups of controls.

SUMMARY AND CONCLUSIONS

(1) A study of enuresis—defined as repeated involuntary micturition after the fourth year of life in the absence of gross organic lesions of causal significance—is made on the basis of a representative series of 1,992 elementary-school children, all cases being about seven years of age. The material is analysed with regard to certain physical, mental, and social factors possibly of importance as causes of enuresis or otherwise associated with it. In the calculations as to social group and intellectual level the 219 enuretic children were compared with the 1,773 non-enuretic children. As regards the other factors that were analysed, a series of 152 enuretic children—96 cases with nocturnal enuresis only, 35 cases with nocturnal as well as diurnal enuresis, and 21 with diurnal enuresis only—was selected and compared with a series of 152 non-enuretic control cases. The two series were matched pair by pair with regard to sex, form at school, and social group. The

TABLE 20

Age Difference versus Child Succeeding in Birth Series: Matched Material.

Enuresis	Age Difference	Enuretics	Controls
Nocturnal	Less than one year	—	—
	1–2 years	11	18
	2–3 years	16	12
	3–4 years	11	6
	4 years or more .... (only children included)	58	60
	Total	96	96
Nocturnal and Diurnal	Less than one year	2	—
	1–2 years	9	5
	2–3 years	3	5
	3–4 years	6	6
	4 years or more .... (only children included)	15	19
	Total	35	35
Diurnal	Less than one year	—	—
	1–2 years	2	—
	2–3 years	4	5
	3–4 years	3	1
	4 years ore more .... (only children included)	12	15
	Total	21	21
Total	Less than one year	2	—
	1–2 years	22	23
	2–3 years	23	22
	3–4 years	20	13
	4 years or more .... (only children included)	85	94
	Total	152	152

investigations were carried out with the aid of a questionnaire that was sent to the children's parents, and of the "health cards" of the schools. The latter are based partly on the results of personal examinations of the children and on interviews with their parents performed by the school-physicians. It is obvious that the methods of examination do not permit closer analysis of the children's mental condition and environment. Therefore, factors of importance for enuresis may have been overlooked. None the less, certain positive results were obtained.

(2) In no case of the present series there was found an organic lesion considered to be the direct cause of the wetting. No association emerged between enuresis and the physical factors that were observed, i.e. significant physical illnesses, neurological disorders, whooping cough during the first two years of life, allergic manifestations, urinary tract disorders, weight at birth, and the physical constitution as assessed by means of the ratio between height and age and between weight and height.

(3) There is no significant difference between the group of enuretics and that of non-enuretics as to the intellectual level as assessed by special group tests.

(4) According to the information obtained from the children's parents there is, in the matched material of the present series, a significantly higher incidence of "nervous" behaviour in the combined group of children with diurnal enuresis with and without concomitant nocturnal enuresis, than in the corresponding group of controls. Furthermore, the observed incidence of speech disorders in the combined group of children with diurnal enuresis is significantly higher than in the corresponding group of controls. As regards the group of cases with nocturnal enuresis versus the corresponding group of controls, no significant differences in the above respects were found.

(5) No significant difference is noted between the groups of enuretics and the respective groups of controls as to the incidence of left-handedness.

(6) There is in the present series a significant difference between the combined group of enuretics and that of controls as to the distribution according to social group, there being in the group of enuretics an under-representation of cases belonging to Social Group I—including the so-called upper classes –and an over-representation of cases belonging to Social Group III—including the working classes. No significant difference was found between the three groups of enuretics, i.e. nocturnal only, nocturnal as well as diurnal, and diurnal only, in this respect. As regards the other social factors that were analysed, i.e. space in homes, broken homes, size of families, position in the birth series, there is no significant difference between the groups of enuretics and those of controls. However, in 6 enuretic cases—5 nocturnal and one diurnal—the wetting started in connection with divorce of the parents or birth of a child in the family.

(7) Hence, the following positive conclusions may be drawn. The investigations indicate that there is a positive association between diurnal enuresis and mental disturbances. It is not, however, feasible on the basis of the present series to draw any conclusions about a pos-

sible causal relationship. On the other hand, in some cases of the present series the wetting started in connexion with environmental changes disturbing the children, suggesting that in some cases in which the children start to wet after a dry period, enuresis is a direct consequence of an emotional disturbance. This applies to nocturnal as well as diurnal enuresis. Furthermore, the investigations indicate that enuresis is more frequent in the lower social strata.

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A COMPARISON BETWEEN COMBINED RESERPINE-CHLORPROMAZINE AND CHLORPROMAZINE THERAPIES IN PSYCHIATRY

By

ARMO HORMIA

In order to compare the combined reserpine-chlorpromazine therapy with chlorpromazine therapy 109 mentally disturbed male patients were investigated. A group of 72 patients were given 400 mg chlorpromazine daily (100 mg × 4). The other group, of 37 patients, were given in addition 4 mg reserpine daily (1 mg × 4). The medicaments were administered orally, in the chlorpromazine group, however, intramuscularly the first two days.

In order to diminish the subsidiary effects which usually appear during the first days both in the reserpine- and especially in the chlorpromazine treatment, the doses were increased slowly. This made it possible for the patients to be up from the very beginning of the treatment, which was considered preferable. In the chlorpromazine group the daily dose mentioned above was reached in a fortnight. In the combined treatment this was the case in eight days.

Next to the psychic effects of the treatment attention was also paid to the somatic effects. Especially the influence of the treatment upon accessory somatic illnesses was followed.

SOMATIC INFLUENCES

The somatic effects of reserpine as well as those of chlorpromazine are for the greater part already known. As our purpose is here to compare on the one hand the somatic effects of chlorpromazine and on the other hand those of reserpine-chlorpromazine, we cannot avoid treating some well-known facts. The somatic effects (Table 1) are small in both groups. In the reserpine-chlorpromazine group the blood pres-

TABLE 1

Comparison between the somatic influences of chlorpromazine treatment and the combined reserpine-chlorpromazine treatment. 0 *= after a 3 weeks' treatment no statistically significant changes could be observed. The value before the arrow = mean value before the treatment. The value after the arrow = mean value after a 3 weeks' treatment. All the changes indicated in the table are statistically significant.* $\varepsilon_{\overline{\Delta}}$ *= standard error in each change.*

		Chlorpromazine therapy		Combined reserpine-chlorpromazine therapy	
			$\varepsilon_{\overline{\Delta}}$		$\varepsilon_{\overline{\Delta}}$
Pulse rate/min.	lying down	0		0	
	standing	0		0	
Breathing rate/min.	lying down	0		0	
	standing	0		0	
Blood pressure	lying down	153/95→130/80	2.3/1.9	/75→71	1.0
	standing	142/97→114/78	2.7/2	/74→68	1.5
Sedimentation rate		0		0	
Blood picture	Haemoglobin	0		88→81	1.2
	Erythrocytes	0		4.7→4.3	0.1
	Leucocytes	0		0	
	Eosinophils	0		0	
Blood sugar		114→102	3.6	0	
Liver function tests	Meulengracht	0		1 :5→1 :3	:0.2
	Thymol.	0		0.07→0.05	0.004
	$ZnSO_4$	0		0.13→0.10	0.004
	Lipoid.	0		0.37→0.30	0.017
	Alk. phosph.	0		0	
Body weight		0		0	

sure before the treatment was rather low. As generally neither reserpine nor chlorpromazine lower the normal blood pressure (*Bein* 1953, *Hormia* 1955) it is clear that the lowering of the blood pressure remains small in this group. In the chlorpromazine group a blood pressure average of 134/76 in a lying position and 116/77 in an upright position was observed after the first day of treatment. This shows that the lowering of the blood pressure caused by chlorpromazine appears totally already during the first day of treatment. Likewise tachycardia appeared in the chlorpromazine group after the first day of treatment (pulse rate in a lying position 90, in an upright position 112/min.) and a retarding of breathing, especially in a lying position (breathing rate in a lying position 11, upright 15/min.). As appears from Table 1, these changes had disappeared after 3 weeks' treatment. This shows that the patients at that time had already become adapted to the treatment and a new physiological equilibrium was reached. In the reserpine-chlorpromazine group no corresponding changes could be observed. In the chlorpromazine group the sedimentation rate was for different reasons high in 40 % of the cases before the treatment. Therefore a slight fall in the sedimentation rate (from 19 to 16) was observed during the treatment. On the normal sedimentation rate, however, chlorpromazine has a rising effect: in cases with a normal sedimentation rate before the treatment a statistically significant rise from 4 to 13 ($\varepsilon_{\triangle} = 1.5$) was observed. Some research-workers suppose that the falling of haemoglobin and erythrocyte values is typical of chlorpromazine (*Chatagnon* and *Torris* 1953). We could not observe these changes in the chlorpromazine- but in the reserpine-chlorpromazine group. It is possible that reserpine there strengthened the influence of chlorpromazine. A remarkable difference between the groups is seen in the liver function tests. During the reserpine-chlorpromazine treatment the values decreased—with the exception of the alkaline phosphatase. In the chlorpromazine group no statistically significant changes were observed, even if the average values became slightly greater.

As appears from the table, no statistically significant changes in the body weight could be observed in either group after the three weeks' treatment. This does not give an exact picture of the influence of the treatment upon the weight, because the increase in body weight typical of both treatments often did not start until a couple of weeks after the beginning of the treatment. The increase in body weight then continued abreast of the psychic recovery. This was the only somatic influence of the treatment which could be observed to correlate with the psychic influences (cf. *Lehmann* and *Hanrahan* 1954). From those patients whose weight increased during the treatment by more than 2 kg, 40 % in the chlorpromazine group were cured completely and only 6 % did not show any improvement. Of the rest of the chlorpromazine group 18 % were cured totally and 22 % did not show any improvement. In the reserpine-chlorpromazine group the values were correspondingly 35 % and 5 %, 0 % and 21 %.

COMPLICATIONS

In the chlorpromazine group a total of 70 different complications and subsidiary effects appeared in 30 patients. In the reserpine-chlorpromazine treatment the number of complications was 19 in 8 patients. A patient who during the treatment showed some complication, was

TABLE 2

Comparison between the complications and subsidiary effects in the chlorpromazine treatment and in the combined reserpine-chlorpromazine treatment.

	Complication	Cases with complications	
		in chlorpromazine therapy (72 cases)	in reserpine-chlorpromazine therapy (37 cases)
I. Complications, which are common in chlorpromazine as well as in reserpine therapy	Hypotension (and collapse)	9	3
	Parkinsonism	1	3
	Convulsions and tremor	6	1
	Vomiting and gastric pain	4	–
	Oedema	3	–
	Hypersomnia	–	1
	Miosis	Usual, harmless subsidiary effect	
	Nasal congestion	Common, harmless subsidiary effect	
II. Complications, which are usually observed only in chlorpromazine therapy	Fever of short duration	8	–
	Leucocytosis and eosinoph.	1	–
	Thrombophlebitis, embolism	1	–
	Epistaxis	3	2
	Tachycardia	5	–
	Worsening in ecg.	7	3
	Dermatic symptoms	10	1
	Liver function disturbance	5	–
	Intense dryness of mouth	6	–
	Allergy in the staff	3	–
III. – in reserpine therapy	Diarrhoea	1	1
	Excessive salivation	–	4
	Total of cases with complications	30 (42 %)	8 (22 %)

thus in both groups more than on an average susceptible to other complications. In the combined reserpine-chlorpromazine treatment the complications were considerably less evident than in the chlorpromazine group: only 22 % of patients had complications as compared with 42 % in the chlorpromazine group. The incidence of complications in the combined treatment was also less than what is usually seen in reserpine treatment (see e.g. *Flach* 1955). The division of the complications into different subgroups appears from Table 2. From this we see that in the combined treatment reserpine and chlorpromazine have a diminishing influence on the subsidiary effects of each other. This is demonstrated especially clearly in Group II, where the appearance of "chlorpromazine-caused" complications in both treatments are compared. In the combined treatment they are only one fourth of those in the chlorpromazine group. It is especially remarkable that the allergic-toxic complications which are typical of the chlorpromazine treatment: fever, dermatitis, and disturbances of the liver functions did not appear at all in the combined treatment. (As the only dermatic symptom bedsores appeared in one case in connection with hypersomnia.) This does not, however, mean that it should be evident that the allergic-toxic manifestations never appear in the combined treatment. On the contrary, our recent experiences in the ambulatory use of the combined treatment show that the allergic-toxic manifestations can be observed also during the combined treatment even if much less frequently than in the chlorpromazine treatment. The diminishing effect of reserpine and chlorpromazine upon each other's subsidiary effects is clearly seen in the pulse rate: tachycardia typical of chlorpromazine as well as bradycardia typical of reserpine did not appear. In general the pulse lability typical of chlorpromazine did not appear in the combined treatment either. "Reserpine-caused" complications appeared in the combined treatment approximately as much as "chlorpromazine-caused" ones. According to former experiments they are commoner in the reserpine treatment (cf. *Kline* 1954). The complications which are common to both chlorpromazine and reserpine, are given in the first group in Table 2. We note that the medicaments obviously do not enforce each other in these respects, because the appearance of complications is rarer in the combined treatment than in the chlorpromazine treatment. A remarkable exception is Parkinsonism, which in the combined treatment appears almost as often as in the reserpine treatment (cf. *Bleuler* and *Stoll* 1955). Parkinsonism, which often begins with a psychomotor turbulence as its presymptom, and the profuse salivation which is commonly connected with it, show that in the somatic manifestations of the combined treatment the influence of reserpine is rather strong (*Hormia* 1956).

The influence of the treatment upon accessory somatic illnesses.

From what is exposed above it is clear that even in the chlorpromazine group, in which the complication frequency was more considerable, serious complications are rare. However, we see from Table 3 that the combined treatment is less risky to those patients who have accessory somatic illnesses. This is especially the case with patients suffering from hypertension and/or organic heart disease. In this group, in the chlorpromazine treatment, signs of advancing disturbance

TABLE 3

Effect of chlorpromazine therapy and combined reserpine-chlorpromazine therapy upon accessory somatic illnesses.

Accessory somatic illness	Chlorpromazine therapy			Combined reserpine-chlorpromazine therapy		
	Number of patients			Number of patients		
	Total	Somatic illness during therapy		Total	Somatic illness during therapy	
		Deteriorated	Improved		Deteriorated	Improved
Hypertension and/or organic heart failure	17	9	–	14	3	1
Functional neurovegetative disorders	8	–	–	6	–	3
Insufficiency of liver function	4	4	–	1	–	1
Poor general condition	2	2	–	–	–	–
Bronchial asthma	1	–	1	–	–	–
Duodenal ulcer	1	–	1	–	–	–
Thyreotoxicosis	–	–	–	1	–	1

of the cardiovascular system could be observed in half of the cases— even if most of these exacerbations were benign ones. In the combined treatment only one fifth of the corresponding cases had complications, and, besides, in one case the electrocardiogram showed improvement without any specific heart treatment. The group of neurovegetative dystonia also stood the chlorpromazine treatment well, but the combined treatment in half of the cases had a downright improving influence upon the dystonic symptoms.

In both groups there was one case in which liver insufficiency was observed before the treatment. In the case of combined treatment liver function tests showed normal values during the treatment. Together with the above-mentioned observation that liver function tests during the combined treatment show smaller values than before, this case suggests that the combined treatment does not stress the liver. With the patient who was given chlorpromazine treatment, one could on the contrary observe cirrhosis-suspect changes in the liver function tests after a three weeks' treatment. When the treatment was interrupted, the liver function capacity returned to its former level. Moreover, three chronic alcoholics, whose liver function tests before the treatment had been normal, during the treatment showed changes indicating liver function insufficiency.

Exceptionally the chlorpromazine treatment might be more suitable than the combined one for those patients who suffer from bronchial asthma. One asthma-case, which had been resistent to former treatments, improved moderately during chlorpromazine treatment. On the other hand, it has been observed that reserpine treatment can aggravate bronchial asthma (*Hollister* a. o. 1955). With three asthma-patients, who were under ambulatory combined reserpine-chlorpromazine treatment (they do not belong to the material discussed here), we have during the first days of treatment seen an acute exacerbation of symptoms. Chlorpromazine may also possibly be preferable to combined therapy in cases with peptic ulcer. In the group of combined treatment we had no ulcer cases, but in the chlorpromazine group there was one case, in which the ulcer was cured during 4 months' treatment. On the other hand, in the combined treatment the influence of reserpine obviously dominates as regards digestive functions and ulcer recurrences have been reported in the reserpine treatment (*Hollister* a. o. 1955). Further experience is, however, needed to explain these questions.

RESULTS

During the second phase of the combined reserpine-chlorpromazine treatment a slight unrest could be seen in several cases. In three cases this unrest appeared rather strongly, as a subjectively disturbing psychomotor turbulence. These observations show that in the combined treatment the part of reserpine in the psychic influences is obvious (cf. *Kline* 1954). When the third period of the treatment, the period of psychic recovery, had lasted some weeks, the daily doses were reduced. Usually they were at the beginning reduced to one half. In accordance with each case, the treatment was then totally stopped or it was continued in ambulatory form with small doses. The duration of the treatment was in the chlorpromazine group on an average 33 days and in the combined therapy group 28 days. In the group of schizophrenics the duration of treatment was the longest, 6 weeks on an average in both therapy groups. In both groups there was an obvious correlation between the duration of the illness and the therapeutic response. This was also the case between the therapeutic response and the effect of the treatment upon insomnia.

Table 4 shows the results of both groups being compared to each other. In the total material the percentage number of completely improved patients was the same in both therapy groups, slightly more than one fifth of the cases. The better effect of the combined treatment is nevertheless obvious: only in 24 % of the cases a marked improvement was not reached, but in the chlorpromazine treatment this was the case in 44 %. As appears from the table, the results especially in schizophrenia show the combined treatment to be more effective. The duration of the illness was in both groups on an average 2.5 years and also in other respects uniformity between the groups was aimed at. The immediate result of the combined therapy can be considered as a surprisingly favourable. Even all those patients, for whom the thera-

TABLE 4

Comparison of immediate results in chlorpromazine treatment and in combined reserpine-chlorpromazine treatment.

0 = unchanged, + = slightly improved, ++ = considerably improved, +++ = remission.

Diagnosis	Therapeutic response					
	0	+	++	+++	Total	
Schizophrenia ..	2	8	7	1	18	Chlorpromazine
	1	–	9	5	15	Reserpine-chlorpromazine
Depression	1	2	3	2	8	Chlorpromazine
	2	–	4	–	6	Reserpine-chlorpromazine
Paranoia	2	–	2	–	4	Chlorpromazine
	–	2	1	2	5	Reserpine-chlorpromazine
Psychosis	1	2	–	2	5	Chlorpromazine
arteriosclerotica	–	2	1	–	3	Reserpine-chlorpromazine
Psychosis	–	1	7	7	15	Chlorpromazine
ex intoxicatione	–	–	2	–	2	Reserpine-chlorpromazine
Alia	5	8	4	5	22	Chlorpromazine
	1	1	3	1	6	Reserpine-chlorpromazine
Total	11	21	23	17	72	Chlorpromazine
	4	5	20	8	37	Reserpine-chlorpromazine

peutic response was ++ (see Table 4), could be discharged and all of them were able to start working. Nevertheless we ought not to forget that it is as yet too early to evaluate quantitatively effects of chlorpromazine and reserpine on the prognosis of schizophrenia. We have observed the material discussed here during an average of one year after the treatment had ended, and during this time two relapses have occurred in the chlorpromazine and as much as seven in the combined treatment group. These observations show that neither chlorpromazine nor reserpine nor combined treatment is causal therapy for psychic disturbances. In order to prevent relapses it is of importance that the psychic state of the patients is continuously observed. The ambulatory continuation of the treatment is also of material importance in this respect. Unfortunately the cooperation ability, especially of the schizophrenic patients, is insufficient.

In the case of paranoia, too, the therapeutic response in the combined treatment seems to be more favourable.

In Table 4 also the results of the group of depressed patients is shown. It has been observed that chlorpromazine is more effective than reserpine in depressions. Reserpine can even provoke depressed states (see e.g. *Muller et al.* 1955). This being so, it is not surprising that the results of the combined treatment in this group are not better than those of the chlorpromazine treatment, rather on the contrary.

DISCUSSION

Though the material discussed here is rather small, the advantage of the combined reserpine-chlorpromazine treatment as compared with chlorpromazine treatment is obvious. Subsidiary somatic effects and complications appear less in the combined treatment and especially patients who suffer from accessory somatic illnesses usually bear the combined treatment better. In the light of this material it seems that also the therapeutic response is better in the combined therapy group. This is especially the case in schizophrenia. On the other hand in depression the combined therapy has possibly no advantages over chlorpromazine alone.

After these experiments were made, several other studies on the combined treatment with reserpine and chlorpromazine have been published. *Eiber* (1955 a) used the combined therapy in the treatment of hypertension. He also experimented (1955 b) with small doses in the treatment of psychically disturbed patients. His opinion is that results were better than those with either medicament alone. *Lemere* (1955) reported his results of ambulatory combined reserpine-chlorpromazine treatment of psychic disorders. He advises doses in which the relation between reserpine and chlorpromazine is the same as here, i.e. 1:100. He is also of opinion that the medicaments are mutually synergistic. Subsidiary effects were less. *Barsa* and *Kline* (1955) treated psychotic patients by adding to the daily reserpine dose 25–100 mg chlorpromazine. This small additional dose often intensified the therapy in cases which did not respond to reserpine alone. A disadvantage of this addition was the production of allergic-toxic complications in some cases. *Kinross-Wright* (1955) used the combined treatment in cases of psychotic patients who had been resistent to chlorpromazine or reserpine alone. In half of the schizophrenic patients he obtained great improvement or remission. In depressions the combined treatment proved rather inefficient. These observations are in accordance with the results mentioned above.

SUMMARY

A comparison between combined reserpine-chlorpromazine and chlorpromazine therapies was established in a material of 109 men-

tally disturbed male patients. The somatic effects of the treatment were followed, and attention was especially paid to the effect of the treatment on accessory somatic illnesses.

In the combined treatment the complication frequency was remarkably less. Especially the allergic-toxic complications characteristic of chlorpromazine therapy seem to be reduced considerably. Patients with accessory somatic illnesses stood the combined therapy better. The results indicate that the therapeutic response in the combined therapy is better than in chlorpromazine therapy. This is especially the case in schizophrenia. On the other hand, chlorpromazine therapy may possibly be preferred in depressions which are not due to organic causes.

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AN ATTEMPT AT EVALUATING THE CONTENTS OF THE CONCEPT OF ACTUAL NEUROSIS

By

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The concept of actual neurosis was set up by *Freud* in 1895. It included the asthenic and the anxiety neuroses, and later (1912–14) *Freud* was inclined to place hypocondria, a syndrome which, however, in itself is very vaguely defined, under the same collective concept as well.

However, it appeared—in a certain way in accordance with *Freud*'s formulation of the mainly somatic background of the actual neuroses—that the psychoanalytic treatment and theory during the following years almost exclusively derived its material from the other main group of neuroses, viz. the psychoneuroses (or transference neuroses), i.e. hysteria, anxiety hysteria, and compulsion neuroses. In connexion with these psychoneuroses we may also mention the neurotic characters, of which the psycho-analytic observations have supplied considerably greater knowledge. The analysts have only in recent years shown increasing interest also in psychoses, the prepsychotic states (borderline cases), and the very actual neuroses. The purpose of the following communication is to sketch an evaluation today of the delimitation and genesis of the actual neurotic syndromes, their symptomatology and therapy in broad outline, as well as their relation to other psychiatric disorders.

Freud considered the actual neuroses to be widely different from the psychoneuroses and, as already indicated, he was of opinion that the genesis of the actual neuroses was mainly of a physiological character. Later concepts such as pathoneuroses, somatoneuroses, vegeta-

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tive neuroses have on the whole been considered synonyms of the concept of actual neurosis.

According to *Freud* the actual neuroses could not be successfully subjected to a psychological analysis, just as *that* differentiated defence which was found then and later to a still wider extent has been found and described in the case of the psychoneuroses, such as repression, displacement, conversion, reaction formation, etc., apparently did not manifest itself in the actual neuroses.

In immediate continuation of the delimitation of the asthenic and the anxiety neuroses *Freud* (1895) advanced his first theory of anxiety, in which he claimed that anxiety must be considered to be conditioned by a kind of poisoning, a libido stasis, which again was a consequence of a blockade of the motory and secretory expression apparatus. The organism in certain situations was overwhelmed by instinctual energy which could not be discharged, and *Freud,* who at that time was almost exclusively preoccupied with sexual energy was of opinion that e.g. coitus interruptus or continual sexual abstinence might result in anxiety neuroses, just as excessive masturbation should be able to result in asthenic neuroses, the chief genetic intermediate links in every case being just considered to be disturbances in the sexual chemistry. In so far we here find an introduction to the later hormonal era.

In 1925, *Freud,* however, acknowledged that he had not himself had any possibilities of further research into actual-neurotic states, and no other investigators at that time and for that matter not later, either—at any rate on a broad basis, at the same time psychological and somatic—had made any more comprehensive systematic studies concentrated on this subject.

But anxiety in itself is not only an actual-neurotic phenomenon, it is simply a central, relatively basal symptom within psychiatry as a whole and perhaps within all medicine. In 1926 *Freud* published his valuable paper on "Hemmung, Symptom und Angst", in which he set up his second theory of anxiety, having a few years previously worked out the part of the psychoanalytic theory which deals with the structuralization of the personality into functional sets connected with those parts which *Freud* termed the id, the ego, and the superego. It is worth emphasizing that *Freud* with his second theory of anxiety did not completely abandon his first theory. Anxiety in the second theory was considered a reaction of the ego either to a traumatic situation or to a situation of danger. In this connexion a trauma is to be understood as so overwhelming an excitation that the person who is actually exposed to it has his stimulus barrier broken, and he will then "automatically", spontaneously, passively be overwhelmed by a pronounced helplessness. A situation of danger exists when the person, thanks to, amongst other things, the greater maturity and preparedness of the ego expects a traumatic situation. When a danger appears (e.g. the separation of the child from the mother, a risk of castration, an incipient, relatively unneutralized breaking through of drives to the consciousness, or an overwhelming pressure of the superergo), the ego, still according to *Freud*, will actively produce anxiety as a signal, an anticipation of the trauma, and a number of defence mechanisms will be activated against these dangers as well as against the anxiety itself.

In psychoanalytic terminology such forms of anxiety are denoted as traumatic anxiety and signal anxiety, and they have been considered as widely different as actual neuroses and psychoneuroses. In this field, however, intensive investigations have been made during recent years. *Schur* (1953) (in support of other authors) is not, e.g., of opinion that we have to do with a purely somatogenetic ("automatic") anxiety. Thus, if an injection of adrenalin provokes anxiety, this result will be expressive of the reaction of the ego to the effects which the adrenalin has otherwise produced within the organism. *Schur* also emphasizes the importance of the ego-regression for both the way in which the danger is experienced and the somatic phenomena entering into the anxiety syndrome in a wide sense of the term. These (somatic) anxiety equivalents may very well in themselves be relatively characteristic, but they are not specific of anxiety in itself (*Brenner* 1953). The same physiological syndrome may be seen e.g. in cases of pain, aversion, rage, which, for that matter, means a material handicap when in so significant a field of symptoms we are to draw conclusions from experimental so-called neuroses in animals to neuroses in man. *Rangell* (1955) is always inclined to consider anxiety as a reaction to danger, viz. a danger that the provoked helplessness will be worse or that it will persist and never cease. But the weaker the ego-structure, the less differentiated defence mechanisms, and the less blocked possibilities of discharge exist, the greater is the chance that the individual will be overwhelmed by inward and outward stimuli and perhaps only be thrown upon a mainly passive endurance. However, according to *Rangell* there is no essential difference between traumatic, more passive anxiety and the more active anxiety. Everything considered, anxiety is not something which is actively produced, but a state of a affect which is experienced, and which perhaps is used by the ego as a motive for defence of the security and integrity of the personality and the possible further consequences of which are borne by the organism as a whole. Physiological tension, processes of discharge, irritability, or reflexological reactions may exist without psychological contents, anxiety never. Anxiety is unimaginable without a further psychological elaboration.

The reason why I have dwelt relatively long on anxiety as such is that the discussion of this question of course has become of decisive importance for the incipient study (also and not least) of the actual neuroses. The investigators who have not downright denied or ignored the existence of the actual neuroses, indeed, have gradually tried to find out whether there should really be a decisive difference between actual neuroses and psychoneuroses and have first of all tried to prove or disprove whether both groups of syndromes could not to a wide extent be understood from the viewpoint of the intrapsychic structural conflict, viz. a conflict between drives and instinctual derivatives on the one hand and ego and superego functions of an inhibiting, defensive, or checking nature on the other. Furthermore the investigators have to a less degree been interested in the strength of the trauma than in its special or relatively special quality and in this way its importance for the reactivation of unconscious conflict.

Indeed, it has already appeared that such unconscious conflicts play a great part or even a very great part both in the case of e.g. the asthenic neuroses and the anxiety neuroses, just as it has been observed that the large number of single symptoms here to a considerable extent could be reduced by a (lengthy) psychoanalytic treatment, through which e.g. an unconscious sense of guilt was neutralized. *Glover* (1949) furthermore states that by psychoanalytic treatment of these forms of neuroses we come across unconscious factors closely corresponding to those found in compulsion neuroses, e.g. strong homosexual fixation, regression to the anal-sadistic plane, and conflict due to aggressivity. *Fenichel* (1945) expresses the same view: The general inhibition found in the case of the actual neuroses must be considered a constant attempt at keeping down dangerous impulses, and if no more especial psychological working up of the inner tension (which again has been brought about by inward or outward excitation), these actual neurotic syndromes will just arise. The question why such a working up does not take place, is, however, left open by *Fenichel*.

We might adduce another example, the historical, more concrete example: masturbation as a genetic factor. A long time ago it has become known to everybody that masturbation does not in itself provoke somatic changes in the organism, but if masturbation is still pathological or pathogenic, it is now assumed that this is connected with the fact that the ego in the situation in question because of the underlying conflict is incapable of checking or securing discharge of tension. Such a masturbation then may be considered a defence against anxiety or as a discharge of pregenital impulses through genital activity (cf. e.g. *Annie Reich* 1951).

My statements so far must suffice to establish that the actual neuroses cannot be understood from a dynamic-mental economic consideration only, a genetic-structural consideration is just as necessary. Here, too, actual conflicts are interwoven with and to a more or less pronounced degree determined by the presence of fundamental conflicts. It is probable that an intrapsychic conflictual basis is a *conditio sine qua non* as regards the question whether a certain libido or aggression stasis which is not made the object of a further psychological working-up, passes into or remains as actual-neurotic states.

In my opinion the reason why the actual neuroses have not been taken up for a closer psychological evaluation to only a fairly similar extent to the psychoneuroses is hardly that those neuroses should be so much more biologically conditioned and so much less psychogenically characterized as the psychoneuroses. In the first place it is rather due to the fact that actual neuroses mainly represent more regressive states than the psychoneuroses, and in the second place the fact that actual neuroses first of all in a psychological respect are much more colourless, at the same time less immediately interesting and more difficult to analyse; in the third place, the actual neuroses have a pronouncedly remittent or intermittent spontaneous course, which may disguise a chronic, more connected historical course, just as they apparently react more easily to different forms of symptomatic treatment such as short-time psychotherapy or (even) treatment with sedatives.

"They teach us nothing," said *Brill* downright as late as 1944, viz. about the actual neuroses, still compared with the more instructive psychoneuroses, which require protracted treatment. But in this connexion it might be stated, as *Brill* does not, that the less instructive might very well also be a consequence of the limitation of the possibilities of psychological investigation available at any time and the methods of examination actually used.

My interest in actual-neurotic syndromes have especially been aroused in connexion with some investigations made by me into a clinically determined group of psychosomatic patients, viz. male patients with duodenal ulcer. It appeared that the patients with duodenal ulcer as compared with an adequate control group were significantly more frequently manifestly neurotic. At the same time it has been possible to establish that practically all neuroses in the ulcer patients belonged to the actual-neurotic type, while regular psychoneuroses were of extremely rare occurrence. Besides asthenic and anxiety neuroses dysphoric states were observed, which for various reasons that will not be discussed in detail here, I include among the actual neuroses.

By penetrating more deeply into the personality functions of the propositi through the comparative investigations made, I think that the following facts important in this connexion have been substantiated: (1) the ulcer patients have a great, in relation to the controls a significantly greater, preparedness for conflict. (2) This preparedness seems to be confined behind inhibitions of a more diffuse, undifferentiated, general, and undoubtedly more regressive nature than is generally seen in the case of psychoneuroses. The ulcer patients in relation to the controls are more inhibited as regards feeling and imagination, a fact (which, as far as I can see, has not been much favoured by investigations especially in a genetic respect within clinical psychiatry) that test-psychologically as well may be confirmed, as the Rohrschach investigations show a greater coartation and tendency towards coartation within the ulcer material, i.e. a restriction of the experience balance rendered by the ratio between movement responses and colour responses (B: Fb = 0–1: 0–1). The dominant traits of the ulcer personalities on the whole are of an obsessional, perfectionistic, expansion inhibited character which exists while the patients, as stated above, do not show any compulsion-neurotic symptoms worth mentioning.

These findings, the closer and further, theoretical and practical basis of which I shall not describe here, have led me to the following considerations:

When there is a great intrapsychic preparedness for conflict, and when, at the same time, perhaps as a consequence, there is a libido and aggression stasis, a relatively general inhibition, a retention of the emotional and imaginative life, of processes of thinking and the psychomotory discharge channels, we shall, e.g. if a psychoprovocation furthermore increases this coartated preparedness for conflict, not see an elaboration of regular psychoneurotic symptoms, but of actual neuroses, including possibly psychosomatic syndromes (perhaps prepsychotic symptoms or psychoses of such a type as depression or catatonic stupor).

The term of stimulus barrier of the personality, which is frequently used, denotes the generally less differentiated and differentiable functions of adaptation which are brought into action against outward or inward stimuli. If this barrier is looked at exclusively so to say from within, I think it may be described better as a *retention barrier* which is assumed to include *preliminary stages of the defence mechanisms.*

The functions falling under both the more basal, regressive, physiologically stamped stimulus and retention barriers and the more differentiated, integrated defence mechanisms amongst other things serve to work up instinctual tension, control it or provide a suitable discharge of it—on the basis of the principle of reality.

Through my investigations of the ulcer patients and through psychoanalytic treatment of neurotics—from which no concrete casuistic material will be adduced here, either—I think it possible to establish that actual neuroses represent a group of neuroses the symptoms of which have their own relatively specific clinical character *and* at the same time the dynamics and genesis of which display a decisive distinctive character, viz. the retentive character in the sense described above. Most actual neuroses, probably all, are to be considered *coartated conflict neuroses.*

I should like in what follows to throw light on the opportuneness of possibly retaining the concept of actual neurosis itself. For is it not a contradiction in terms to speak about neurosis actualis if the "premorbid" personality structure here, too, is of decisive importance for the appearance of the syndrome?

As to this it may be said, in the first place, that the provoking factors in the case of the actual neuroses are really often of a remarkable order of magnitude. A dramatic single trauma or an accumulation of such traumatic influences *can* manifest itself. This is especially seen in cases of traumatic neuroses (e.g. war neuroses or fright neuroses). *Freud* (1926), however, was doubtful as to the question whether a concrete traumatic experience as it were in itself should be able to produce a neurosis in adults at all, and most modern authors agree that psychotraumatic influences, also in cases of traumatic neurosis, are not defined so much by their conspicuous quantity and the break of the stimulus barrier caused in this way, as by their special quality and its relevant importance as mobilizer of unconscious conflict situations within the personality (cf. e.g. *Simmel* 1944, *Sperling* 1946, *Brenner* 1953).

Secondly, the provocation of actual neuroses plays a relatively more dominant, significant role also in the way that the types of personality who get actual neuroses, as a rule are quiet and comparatively conformal; they have previously on the whole *seemed* little neurotic. On this background the immediate trauma therefore will frequently appear with the greater conspicuousness. On closer evaluation the releasing event will, however, often also here appear to be a screen precipitation in the sense that the stress is less caused from outside than striven after from within, viz. through a prolonged interplay between environment and projecting or provoking factors, e.g. as an element in a masochistic personality structure. The manifestations seen in the actual neuroses are not very rarely of the acting-out type, i.e. there appears a partial instinctual discharge provoked by an actual situation, as if the latter to the patient were identical with a previous significant situation or simply identical with *that* original situation which formed the pattern of need or conflict. This acting-out might also be described as a case in which primitive material is discharged through a rupture in the retention barrier, as a short circulation in which the material is not confronted with and transformed by the personality functions which mainly belong to the ego-structure.

In the third place, it should be emphasized that even though the premorbid personality structure into the background of which of course both heredogenetic and early psychogenetic factors enter, naturally play a very great role in cases of actual neurosis, there is still in these cases frequently a very close connexion between the person's actual somatic and psychical state in the widest sense of the term and the symptomatology which will belong to the actual neurosis in question. I have mentioned some grounds for including psychosomatic syndromes in the group of actual neuroses, psychosomatic syndromes in a strict sense, i.e. such somatic diseases, the early and continuous fundamental pathogenetic elements of which *are,* and the provocation of which *may be,* of mainly an emotional character. The somatic condition may be decisive of the question what psychosomatic form of appearance a preparedness for conflict of a certain order of magnitude will assume. A person with a comparatively early developed achylia, e.g. as part of a pernicious anaemia, will not, of course, get a duodenal ulcer, however susceptible to it he might be from other somatic influences and from the whole of the outward and inward situation. In the relevant genesis of the actual neuroses it is also possible to come across psychotraumatic influences due to an obtrusive experience in the patient of different irreversible somatic defects in himself, e.g. amputation, blindness, deafness, presenile and senile reduction of various organic processes. Such factors may be continuous, latently chronic, always real traumata resulting in actual neuroses, if there are not at the same time rich possibilities of adaptation on the basis of a previously given and (otherwise) still well-preserved elastic personality.

For these three reasons: the quantitative and the relatively pregnant role of the provocation and the importance of the actual psychical and somatic state in a wide sense of the term, I still find it reasonable, even if all the three reasons were accompanied by supplementary reservations, to retain the concept of actual neurosis as a warrantable collective concept of the syndromes belonging here. As, however, the genetic conditions in the actual neuroses must be considered different from those originally described by *Freud*, these neuroses might perhaps also be more felicitously described as retention neuroses or coartated conflict neuroses.

The fact that certain primary somatic changes, especially in the nervous system or the endocrine apparatus, may give direct symptoms such as asthenia or perhaps apathy or dysphorias, does not justify an inclusion of such somatogenetic syndromes among actual neuroses, even though they will often be complicated with or later completely develop into actual-neurotic states.

The apathic syndrome, the investigation and description of which is also a neglected field within clinical psychiatry, is as a rule an actual-neurotic state. The indolent and flegmatic, dull, colourless, and stereotyped is interpreted as a defence reaction to aggressive impulses (*Freud* 1926, *Fenichel* 1945, *Greenson* 1949, 1953). Besides negation and repression a coartation no doubt also enters in this defence. Besides, in apathy there is also a more or less pronounced inhibition of the perception processes, and so we approach to the prepsychotic or psychotic states.

According to what has been stated above, the actual neuroses are on the whole to be considered more regressive phenomena than the psychoneuroses. This is especially observed during the psychoanalytic treatment. Actual-neurotic patients are undoubtedly more narcissistic; but if the analyst realizes contact with them on this narcissistic basis, they will often quickly produce a rich, primitive material in the transference. They will easily proceed to transference, but a greater art and experience is needed to adjust this at a suitable level than is generally seen in the psychoneuroses. In the actual neuroses the character deviations are of a more rigid character, and aggressivity (and fear of retaliation) on the whole play a greater part. During the treatment of actual neuroses psychoneurotic symptoms appear in the transference neurosis.

The actual neuroses must chiefly be considered as placed between the classical psychoneuroses on the progressive side and the prepsychoses and psychoses on the regressive side. We must be aware of the fact that a more resistant, continuous, clinically diagnosed, actual-neurotic syndrome may cover a considerable prepsychotic or psychotic predisposition.

It has been maintained that psychoneuroses have become rarer during the last few decades; sure statistics are not, however, available. On the other hand, it is a fact that a psychosomatic disease such as duodenal ulcer has actually became more frequent in men since about the first World War, and thus this is not only due to improved diagnostics, but in the same way as psychosomatic medicine, still in a strict sense of the term, has entered a new era thanks to our improved physiological and psychological methods of examination, I also think it may be stated about the actual neuroses in general that they have become actual in a new way, because our recognition of them has increased. On the other hand, we know nothing definite at all about the question whether there is a real increase in the number of cases of actual neurosis.

The fact that actual neuroses are conflict syndromes of course causes that further psychoanalytic investigation into them will in principle be as important as it has been and still is as regards the psychoneuroses. It is certain that psychoanalytic treatment can be given successfully to certain chronicized actual neuroses, but the indication as regards a classical form of psychoanalytic treatment must be still more cautious than in the psychoneuroses.

When it is maintained that certain new drugs, e.g. suavitil, should produce a good effect on neuroses, the reference is presumably to the actual neuroses. And when it is stated in speech and writing that these sedatives, the effect of which is probably of a purely inhibiting, retaining nature, should facilitate the psychotherapeutic method, it should be kept in mind that indeed it can only be a question of the supporting, covering forms of psychotherapy, in which a cathartic therapy of short duration must also be included. The fact that chlorpromazine and serpasil can damp down certain psychotic symptoms to a clinically more or less latent psychotic or quasi-actual-neurotic state, must of course, even though it is only symptomatic, be characterized as an extremely significant result of treatment. Indeed, it is possible that psychoneuroses proper may in the same way medicamentarily be changed into a kind of actual-neurotic state, but such a manoeuvre, according to what has been stated above, can hardly be considered an advantage, unless, when no other treatment is possible, a suitable apathy in these patients is preferred to a certain fertility in traits of personality and in symptomatology.

SUMMARY

Actual neuroses (in adults) include various subgroups: the traumatic neuroses and asthenic, anxiety, dysphoric, apathic, psychosomatic, and certain hypochondriac syndromes. Actual neuroses must be considered frequent and important mental disorders. They appear in

cases of an overwhelming psychotraumatic influence on the personality or—much more frequently—in personality types, preferably poor in symptoms, mainly obsessional, but otherwise widely different, who in cases of different stress and consequently an increased coartated preparedness for conflicts develop a changing actual-neurotic symptomatology which may often be dependent on the actual somatic state as well. Actual neuroses, or as on the basis of their special clinics, dynamics, *and* genesis, they might be more felicitously termed: retention neuroses, must, as regards their development, have their point of gravity placed between the classical psychoneuroses on the one hand and prepsychoses and regular psychoses on the other. The actual neuroses can be treated symptomatically with supporting psychotherapy and sociotherapy besides medicamentarily, but in their further investigation and in cases in which radical treatment is possible, psychoanalytical methods should in all probability be used. In the case of the psychosomatic syndromes, however, these methods must of course be further supplemented by the somatic technique of examination and therapy adequate in the individual cases.

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COLORIMETRIC ESTIMATION OF SUCCINIC DEHYDROGENASE ACTIVITY IN THE RABBIT BRAIN WITH TETRAZOLIUM SALT

By

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INTRODUCTION

The reduction of tetrazolium salts has been widely used as an indicator of viability and as a measure of metabolic activity in both animal and plant tissues. *Straus, Cheronic & Straus* (1948) used the salts for demonstration of reducing enzyme in both *in vivo* and *in vitro* experiments and reported on its toxicity. *Black & Kleiner* (1949) pointed out the applicability of tetrazolium salt in the study of tissue metabolism and of the effect of enzyme inhibitor. Histochemical detection of dehydrogenases by adding the corresponding substrata to the reaction medium, including tetrazolium salt, was demonstrated by *Seligman & Rutenburg* (1951) on succinic dehydrogenase, and *Dianzani* (1953) applied this method for the detection of lactic-, α-glycerophosphate-, malic dehydrogenase and d-aminoacid oxidase. *Shelton & Schneider* (1952) showed the usefulness of various tetrazolium derivatives as histochemical indicator of dehydrogenase activity and particularly examined the localization of formazan compounds in the cell.

Besides, *Kun & Abood* (1949) and *Glock & Jensen* (1953) established a new convenient method by which the succinic dehydrogenase activity of tissue homogenate could be estimated with tetrazolium salt and stated that this technique had some advantages in that the reaction system required no anerobic condition and enzyme activity was determined colorimetrically.

The present experiments were undertaken for the colorimetric determination of the distribution of succinic dehydrogenase activity in the homogenate of the brain of the rabbit.

EXPERIMENTAL

The brain removed immediately after the animals were killed was washed with ice-cold Ringer solution, weighed and homogenized in a Waring Blender with 10 times its volume of water at 0° C.–3° C.

Succinic dehydrogenase activity was estimated in a Thunberg tube containing a reaction mixture composed as follows:

For the main tube:

0.1 M.	Phosphate buffer (PH 7.4)	1.0 ml.
10 %	Homogenate	1.0 ml.
	Water	1.0 ml.

For the side arm:

2×10^{-3} M.	2,3,5,-Triphenyltetrazolium chloride (TTC) solution	1.0 ml.
0.1 M.	Sod. succinate solution	1.0 ml.

The tube, evacuated and flushed with nitrogen three times, was kept in a water bath at 38° C. After 10 min. of preliminary incubation, the content of the side arm was tipped into the main tube and the mixture was further incubated.

When the incubation was completed, 0.5 ml. 20 % trichloracetic acid and 10 ml. ethyl acetate were added and the tube was stoppered and shaken vigorously for complete extraction of the triphenylformazan (TPF) formed.

After centrifugation, the colour density of the ethyl acetate layer was read from a Shimazu electrophotometer at 470 mμ.

RESULTS AND DISCUSSION

The results obtained are summarized in Figs. 1–4 and Tables 1–3. Fig. 1 shows the visible absorption spectrum of TPF formed by the reduction of an aqueous solution of TTC (300 γ/5 ml.) with a few crystals of sodium hydrosulphite and extracted with ethyl acetate. The maximum absorption band is at about 485 mμ.

A calibration curve was prepared by reducing variable amounts of TTC with sodium hydrosulphite under the same experimental conditions as above. The results (Fig. 2) show a linear correlation between the concentration of TTC used and the optical density when reduction was completed. *Kun & Abood* (1949) have reached the same results with acetone extract of TPF in concentration ranging from 20 to 300 μg. at 420 mμ.

The reduction rate of TTC changing in the course of time and in different experimental conditions is illustrated in Figs. 3. When the homogenate was incubated without succinate, no reduction of TTC oc-

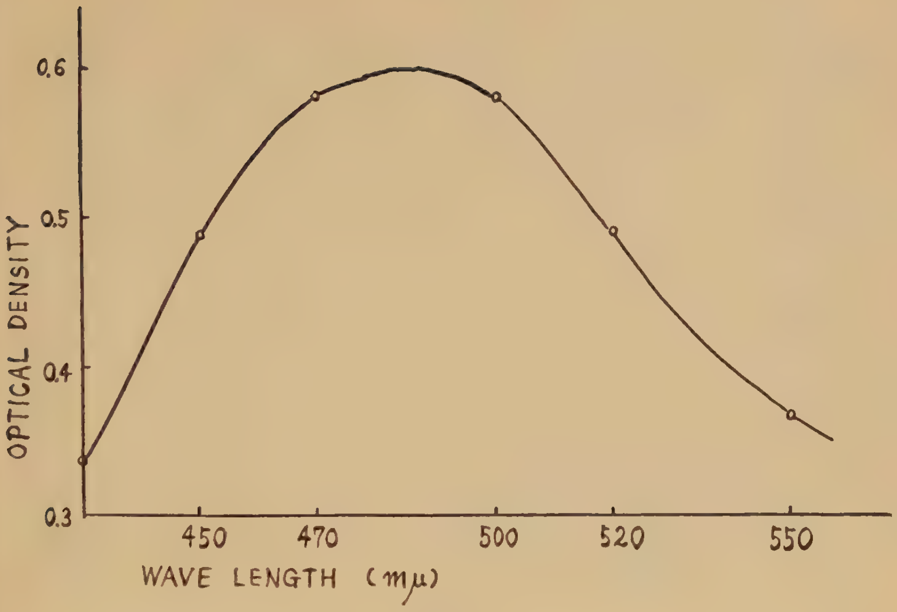

Fig. 1.
Absorption Spectrum of Reduced TTC.
300 γ/5 ml. TTC solution is reduced with sod. hydrosulphite and extracted with 10 ml. ethyl acetate for measurement of color density.

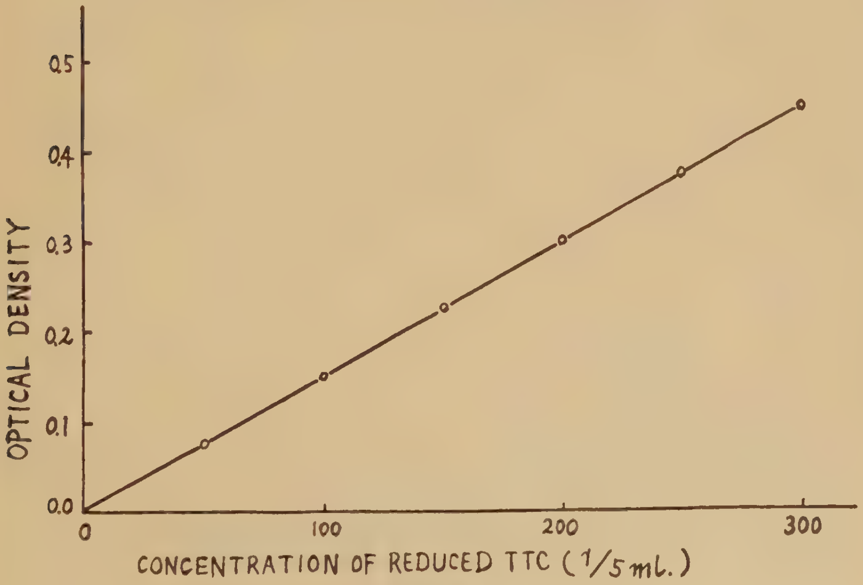

Fig. 2.
Calibration Curve.
Fixed increments of TTC are reduced with sod. hydrosulphite and extracted with 10 ml. ethyl acetate for measurement of color density through a 470 m μ filter.

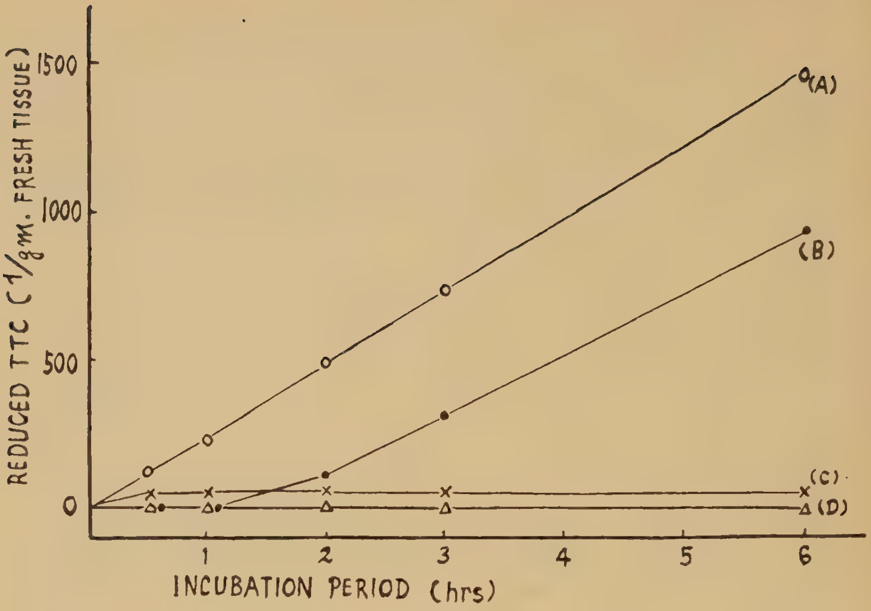

Fig. 3.

Reduction Rate of TTC in Various Experimental Conditions.
Curve A: anaerobic, with substratum, Curve B: aerobic, with substratum,
Curve C: anaerobic, without substratum, Curve D: aerobic, without substratum.
Other details are described in the text.

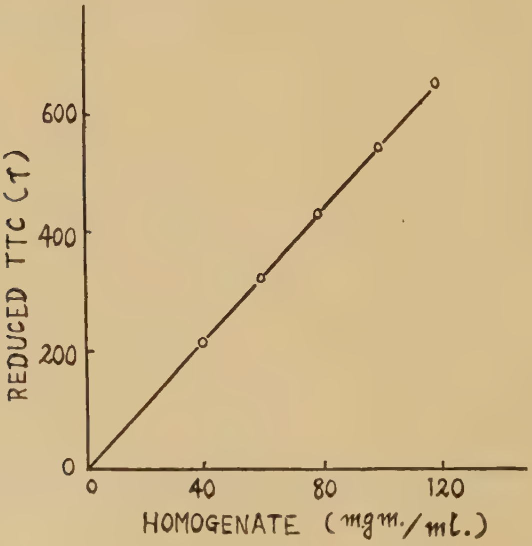

Fig. 4.

Relation between the Reduction Rate and the Amount of Homogenate.
Fixed increments of rabbit-brain homogenate are incubated with 2 mg. TTC in 0.1 M phosphate buffer (PH 7.4) for 2 hrs. at 38° C. The TFP is extracted with 10 ml ethyl acetate for measurement of colour density through a 470 m μ filter.

TABLE 1

Reduction Rate of TTC in Brain, Kidney, and Liver
(expressed in reduced TTC γ/gm. fresh tissue).

Incubation period in min.	No. of case	Brain	Kidney	Liver
30	1	160	900	740
	2	120	1110	690
120	1	420	2620	2020
	2	350	2620	1980

TABLE 2

Reduction Rate of TTC in Different Parts of the Brain
(expressed in reduced TTC γ/gm. fresh tissue).

Incubation period in min.	No. of case	Cerebrum	Cerebellum	Brain stem	Spinal cord
30	1	310	310	220	160
	2	280	350	240	160
120	1	600	620	510	470
	2	510	580	590	510

TABLE 3

Reduction Rate of TTC in the White Matter and the Grey Matter of the Cerebrum
(expressed in reduced TTC γ/gm. fresh tissue).

Incubation period in min.	No. of case	White matter	Grey matter
30	1	185	105
	2	160	90
120	1	610	340
	2	595	325

curred aerobically (Curve D), but under anaerobic conditions only a small reduction was induced at a rate almost constant during the full incubation period (Curve C). Thus the endogenous dehydrogenase activity was not demonstrated in these experimental conditions. But in contrast to the results obtained with homogenate, brain tissue block incubated in the same medium without succinate, either aerobically or anaerobically, was stained reddish macroscopically within 1–2 hrs., indicating the reduction of TTC, and another block incubated in the same medium with succinate was stained deeper.

In comparing Curve A and B, it will be clearly seen that the reduction rate of TTC was higher under anaerobic conditions than under aerobic ones. This finding, that oxygen competes with TTC as a hydrogen acceptor, agrees with that of *Rutenburg, Gofstein, & Seligman* (1950).

It has already been reported by many workers that the reduction of TTC with tissue homogenate is accelerated by the addition of a specific substratum to the reaction medium, *Rutenburg, Gofstein, & Seligman* (1950) using succinate, malate and lactate, as substrata, *Kun & Abood* (1949) and *Glock & Jensen* (1953) succinate. The specific enzymatic system may thus be demonstrated by this procedure. In this experiment, Curve A, as compared with Curve C, indicates the specificity of the substratum confirming the validity of the above finding.

Furthermore, the straight linear correlation between the amount of homogenate and that of reduced TTC is shown in Fig. 4, only that in this experiment 20 % homogenate is used instead of 10 %.

On the basis of these findings the succinic dehydrogenase activity was determined in the following manner. The colorimeter was adjusted to zero with a tube from which only the substratum was omitted.

As examined in three different organs (Table 1), succinic dehydrogenase was going on in decreasing order of activity in kidney, liver and brain, reaching in liver and brain about 75 % and 15 %, respectively, of its activity in the kidney. This finding is coincidental with that of *Rutenburg, Gofstein, & Seligman* (1950).

As far as I know, there has been no report in the literature on the succinic dehydrogenase activity in the different parts of the brain. As indicated in Table 2, the activity is the greatest in the cerebellum, followed in decreasing order by the brain stem and the spinal cord. It is roughly the same or slightly lower in the cerebrum than in the cerebellum.

Moreover, the reduction rate of TTC was higher in the white matter of the cerebrum than in the grey matter, as shown in Table 3. The activity in the latter is only 51–57 % of that in the former. This finding was supported by the observation that the tissue block incubated in the same medium is stained faster and more deeply in the white matter than in the grey matter.

SUMMARY

Succinic dehydrogenase activity in the homogenate of the brain of the rabbit was measured colorimetrically with TTC. Liver and brain were found to have 75 % and 15 %, respectively, of the activity in the

kidney. It was highest in the cerebellum, nearly as much in the cerebrum and next in the brain stem and also in the spinal cord as examined in four different parts of the brain. In the grey matter of the cerebrum there was only 51–57 % activity of that in the white matter.

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ADRENALIN- AND MECHOLYL TEST PERFORMED IN SCHIZOPHRENIA AND SCHIZOPHRENIFORM STATES

By

CARL LUDV. LAANE

From 1949 50 *Funkenstein, Greenblatt* and *Solomon* published their experiments with epinephrine and mecholyl on mentally ill patients in 3 articles in "The American Journal of Psychiatry" (one of them also together with *Root*). Previously, *Freeman* and *Carmichael* (1935), *Hoskins* and *Jellinek* (1934), *Kanner* (1928), and others have found that schizophrenic patients show less reaction to epinephrine than normals. However, *Langfeldt* (1926) has shown that weak or negative adrenalin reactions can be found also in normals, and that it is on the whole difficult to judge adrenalin injections even when they are performed intravenously. Several research-workers have discovered that anxiety can be produced in psychoneurotic patients by epinephrine injections, likewise that this medicament can activate the symptoms in these patients. *Myerson, Loman* and *Dameshek* (1937) have found little change in the mental status of schizophrenic patients after injection of mecholyl.

Funkenstein et al. have in their first work (1949) a material of 115 patients, 32 of whom were psychoneurotics, 37 schizophrenics, 15 psychopathics, 12 with involutional psychosis, 4 manic melancholics, and 15 controls.

They performed their tests during three successive days on patients in the lying-down position. The first day injection of 1 cc. normal saline intramuscularly, the second day 0.05 mg. epinephrine dissolved in ½ cc. distilled water intravenously, given in the course of 1 second. The third day 10 mg. mecholyl dissolved in 1 cc. distilled water intramuscularly. The blood pressure was measured before the injection. Next, the blood pressure was measured every half minute in the course of the first 6 minutes and then every minute for the next 19 minutes, i.e. a total registration of 25 minutes. The results reached by them were then plotted in curves in the coordinate system, with time as the abscissa and blood pressure as the ordinate. In their material they have, generally speaking, found 7 different patterns of curves for epinephrine and mecholyl.

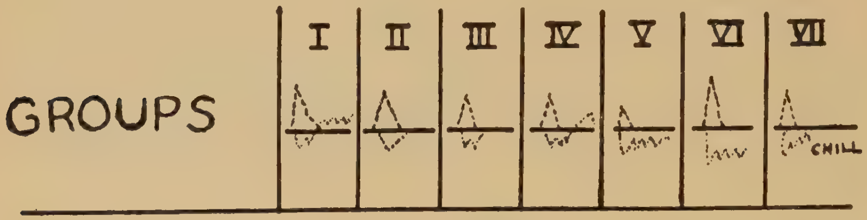

FIG. I.

ADRENALIN CURVE------- MECHOLYL CURVE ········

In their first work *Funkenstein et al.* (1949) found that a total of 20 of the 37 schizophrenic patients had a curve pattern corresponding to Group V, and it is typical of the entire material that none of the other cases (psychoneurotics, psychopathics, manic melancholics, and the controls) had this pattern.

In Group V the epinephrine curve rises about 30 mm. ("mild reaction") and falls to normal again in a minute or two. The reaction to mecholyl is characterized by a relatively rapid fall from e.g. 120 mm. to 90 mm., after which the curve remains comparatively horizontal during the entire period of observation (25 min.), in other words, homeostasis is not re-established in the course of the observation period.

On the whole their findings are characterized by little response to epinephrine and a marked response to mecholyl.

In some cases they found as a reaction to the mecholyl the so-called "chills". These are stated to appear from 11 to 23 minutes after the injection—the patient begins to tremble all over and this trembling is accompanied by "a severe chill" lasting several minutes. 15 of the other schizophrenics belonged to Groups I, II and III. The psychoneurotics were mainly in Groups III, IV, VI and VII. The controls were mainly in Groups II and III.

In their second work *Funkenstein et al.* (1949) explained their experiments with epinephrine and mecholyl and the effect in relation to electric shock treatment. Their material consisted of 24 patients, 8 of whom were schizophrenics. They generally found a decrease in the

The curves in Group V have this appearance:

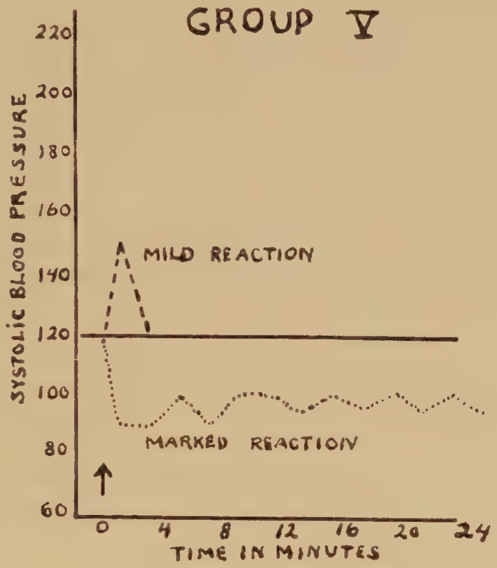

FIG. II

ADRENALIN CURVE ------

MECHOLYL CURVE ....

"resting blood pressure", an increase in the systolic blood pressure after epinephrine and a decrease in the systolic blood pressure response with mecholyl, followed by clinical improvement. The patients who before shock treatment showed anxiety attacks after mecholyl, showed dramatic clinical response to electric shock treatment, with improvement. The patients who before treatment showed a high reaction to epinephrine (80 mm. mercury or more) or who suffered from anxiety attacks with epinephrine, showed no clinical improvement with electric shock. Several patients showed no change in their patterns of response to autonomic medicaments after shock treatment, and these patients did not show any clinical improvement.

In their third work *Funkenstein et al.* (1949) stressed the excellence of this method to show changes in the autonomic nervous system in patients treated with electric shock and thereby for the prognosis. They selected 100 patients from Boston Psychopatic Hospital for shock treatment (48 schizophrenics, 21 manic melancholics, 12 psychoneurotics, 13 with involutional psychosis, and 6 others). They then found that schizophrenia was the only disease group with a pattern from all the

7 previously described pattern groups. However, their schizophrenias had a special affinity for Groups I and III, besides Group V (where they especially found catatonic patients). The manic melancholic patients were found especially in Groups VI and VII, whereas the psychoneurotics were mainly placed in Groups I and VI. On examination it proved that especially Groups VI and VII responded effectively to electric shock treatment. The majority of the patients in Group IV were neurotic. *The experimenters stress that no patterns are specific of definite clinical groups of diseases, and at the same time they stress that if the schizophrenias belong to Groups VI and VII (the same group as manic melancholic patients and involutional psychoses) the condition improves by electric shock treatment. On the other hand, schizophrenias belonging to other groups do not improve.*

Alexander (1955) has studied 201 consecutive patients to whom *Funkenstein*'s prognostic test was applied prior to treatment (electroshock therapy, psychotherapy, and insulin therapy). The subject was to correlate the pretreatment test results with the outcome of therapy. The distribution of autonomic test patterns of the 201 patients studied was as follows: affective psychoses 65 per cent in Group VI and VII and 35 per cent in Groups I to V. In the psychoneuroses, the schizoaffective psychoses and the schizophrenic groups, the cases belonging to Group I to V predominated, ranging from 69 to 72 per cent, while the cases falling into Groups VI and VII ranged from 28 to 31 per cent. His results with respect to recovery and non-recovery are as follows: patients falling into Group I have the best prognosis and it is closely followed by Group VI. Group V had the lowest proportion of recovery. For Group IV he found the recovery rate with psychotherapy equal to that with electroshock therapy.

We have at the University Psychiatric Clinic of Oslo wished to retest the results arrived at with the adrenalin-mecholyl test, especially as regards schizophrenia and the schizophreniform states. As appears from the above, *Funkenstein* and associates have not kept these two groups separate.

We have in this respect chosen a material of 30 "clear cut schizophrenics" for our tests. The method we have used is as follows:

We have *always performed the mecholyl test before the adrenalin test*, and we have let a few days elapse between the two tests. If the adrenalin test is performed first, the adrenalin will, via the hypophysis and the adrenals affect the hormonal apparatus and possibly have a disturbing affect on the other tests. *The mecholyl test* is performed in the morning on an empty stomach and the medicament we have used has been obtained through Rikshospitalet's Chemist in injection flasks of 25 mg. acetyl-β-metyl-cholin-chloride. This is diluted with 5 cc. sterile, distilled water, and 2 cc. of this are drawn up for intramuscular injection. The blood pressure is registered before the injection and the patient lies with the cuff on him during the whole test. After the injection the blood pressure is registered every half minute during the first 3–4 minutes and then every minute for 15 minutes. *In the adrenalin test* a quarter ml. of 1/10 per thousand adrenalin solution is given intravenously. This test is also performed on an empty stomach in the morning, a few days after the mecholyl test. The blood pressure is registered in the same way as in the previous test, and in the case of the adrenalin test an effort is made to register the blood pressure 2–3 times during the first minute and preferably also in the second minute, after which 2 minute intervals suffice.

In order to perform the tests as accurately as possible, and to obtain the best possible results, we have stored the adrenalin solutions in refrigerators, these solutions often being replaced in order not to be too old. We have then made graphs of the results of our findings in the same way as *Funkenstein et al.* The results of these examinations appear from the following.

The test could not be performed on 6 of the patients on account of some unrest and poor cooperation during the test. On 5 patients one test only (the adrenalin test) was performed as the patient was less willing to cooperate in Test 2, so that the results could not be used. (4 of those adrenalin curves correspond to Group V and 1 to Group IV). In 9 cases we have found "coinciding curves" corresponding to the curves of *Funkenstein et al.* 7 of these belong to Group V and 2 to Group III. It has otherwise proved that in 10 cases there was a divergency between the groups for adrenalin and mecholyl in the same patient, so that the patient in question could e.g. be placed in Group V after the adrenalin test and in Group IV after the mecholyl test (4 cases) and in 6 cases there is such a great divergency that Group I or II can be used for the one test and Group V for the other. We have not in any of the patients examined found reaction patterns corresponding to Groups VI and VII, namely the "schizophrenic patients" who by *Funkenstein et al.* are stated to react well to electric shock treatment. This corresponds so far as our 30 are chosen patients of the "clear-cut schizophrenics" who have shown poor reaction to electric shock treatment.

Responses to the mecholyl injection have in most cases been light clinical reactions in the form of reddening of the face, sensation of warmth, light perspiration, increased spit secretion. On the other hand we have only in one or two cases observed slight chills, and in no cases the previously described greater "chills". Great anxiety after mecholyl injection has been negligible.

Responses to the adrenalin injection have in nearly all cases been very slight or there has been no clinical reaction. As a rule the patients felt slight laxity accompanied by slight palpitations, and in some cases they had some pressure on the chest and "felt funny in the head" and showed a slight paling. Anxiety after the injection only occurred in one or two cases and did not give any basis for us to work on. These reactions disappeared fairly fast.

Another material, also consisting of 30 patients belonging to various disease groups, was closely examined. This material consisted of 6 clear-cut schizophrenics, 11 with schizophreniform states, 4 psychopathics, 7 neurotics and 2 with organic brain ailments. The original material was much bigger, but owing to various mistakes in the examination technique only 30 patients were included. The material is small and the results presented here must be judged accordingly.

The results are summarized in the following table.

TABLE I

Results of a study of 30 consecutive patients to whom Funkenstein's prognostic test was applied.

		Groups							Remarks
		I	II	III	IV	V	VI	VII	
Schizophrenia	6		1	3		2			
Schizophreniform states	11			3	1		1		6 of the schizophreniform cases difficult to place in distinct Groups
Psychopathic personality	4		1			3			
Neurosis	7	2	3						On 2 cases one test only performed
Organic case	2		1						1 case difficult to place in a Group

The author has performed a katamnestic revision of the 11 cases which during the stay in the Clinic were diagnosed as "schizophreniform states" and has correlated the results to the treatment and to the clinical condition by re-examination 3 months later. It proved that 3 of the 11 cases of "doubtful" schizophrenias must be classified as genuine schizophrenias. As appears from Table II all the 3 of them now are clinically unchanged. 2 of them were treated with electroshock. Their responses to adrenalin and mecholyl are different. Case no. 3 (see Table II) belongs to Group VI (one of the two prognostically favorable Groups of *Funkenstein*). The two others (Nos. 6 and 11) must be placed in Group V after the adrenalin test. Of the remaining 8 "real schizophreniform cases" (Nos. 1, 2, 4, 5, 7, 8, 9 and 10) 4 cases are difficult to place in distinct groups. All 4 have a pattern of response to adrenalin corresponding to Group V.

TABLE II

11 cases of doubtful schizophrenias classified after katamnestic revised diagnoses and correlated to Funkenstein's tests; treatment and clinical condition at follow-up investigation.

No.	Katamnestic revised diagnosis	Groups		Treatment	Clinical condition at follow-up investigation
		A	M		
1	Schizophreniform ps.	V	—	Not treated	Unchanged
2	Schizophreniform ps.	V	—	8 electroshock	Cured
3	Schizophrenia	VI		6 electroshock	Unchanged
4	Schizophreniform ps.	III		6 electroshock	Unchanged
5	Schizophreniform ps.	III		Not treated	Cured
6	Schizophrenia	V	II	5 electroshock	Unchanged
7	Schizophreniform ps.	V	II	8 electroshock	Improved
8	Schizophreniform ps.	IV		6 electroshock	Improved
9	Schizophreniform ps.	III		Not treated	Cured
10	Schizophreniform ps.	V	II	Not treated	Improved
11	Schizophrenia	V	II	Not treated	Unchanged

Also in this material we have had some difficulties in placing certain cases in a definite group, as there have been divergencies between the groups in which cases ought to be placed after the adrenalin test and after the mecholyl test. On the whole we may say that in this material nothing has come to light which may be considered especially characteristic of the various groups of diseases. We have not found any actual difference in the reaction to the tests between the clear-cut schizophrenics and the schizophreniform states.

Our experiences with the adrenalin and mecholyl tests are as follows:

At the carrying out of these tests many precautionary rules must be observed. The cholin medicaments (mecholyl) always ought to be injected before the adrenalin, and at least one day should elapse between the tests. The mecholyl ought to be stored in a dry, dark place. The test ought to be performed in the morning on an empty stomach with the patient in a lying-down position. The doses injected on all test cases must be of exactly the same size for comparison of results. Likewise it is important that the same blood pressure apparatus is used in all measurings. Absolutely fresh adrenalin solutions should always be used, as thin adrenalin solutions are very inconstant. The solutions must be stored in a refrigerator. The blood pressure registration ought to be performed immediately after the adrenalin injection, as the increase usually takes place rapidly, from 20 seconds up to 1 to 1½ minutes after the injection. The blood pressure therefore ought to be checked as often as possible in the course of the first 2 minutes, after which 2 minute intervals will suffice. Between the readings all air must be expelled from the blood-pressure cuff before it is pumped up again. The rate of injection is also an important factor for the result of the reaction. A change of from 1 to 2 seconds can have considerable consequences. *K. Cyvin* (in press) has stressed that mecholyl injected intramuscularly is hardly expedient for judging the reaction of the organism to the cholin medicaments, as the reabsorption conditions with this application are of the greatest importance to the response of the reaction. Where the reabsorption is speeded up by massaging of the place of injection, the reaction takes place more rapidly than when no massage has been given. The time from the injection until the blood pressure has been stabilized can then in no case be used as a measure of the reaction. *Cyvin* asserts that more accurate results can be obtained if acetylcholin is injected intravenously. With regard to adrenalin there is a great difference between the affect of small and large doses. The dividing line between small and large doses is rather abrupt. The dose we use at the Psychiatric Clinic (25 microgm.) may be considered small for a man of 70–80 kgs., but rather large for a woman who weighs about 50 kgs.

The observations of *Funkenstein et al.* of frequent anxiety reactions to injections of mecholyl or adrenalin, have not been observed in our material. The few cases in which we have observed anxiety (and then only to a very moderate degree), have not corresponded typically to respective improvement or no improvement with electric shock treatment. Furthermore, we have in many cases had difficulties in placing each separate case in the corresponding group for adrenalin and mecholyl. On looking at *Funkenstein*'s classification in 7 groups it will be seen that it will be the result of the mecholyl test which, for example, decides whether a case is to be placed in Groups I, VI or VII, possibly II or III. In some cases there has been a lack of conformity here. Reaction patterns of the type Group VI and VII appear only in 1 case in our material and this patient during his stay at our clinic was treated with 6 electroshocks without recovery and now by re-examination he is found to be a clear-cut schizophrenic. 6 cases among the 11 "schizophrenic states" (the 6 cases who were difficult to place in distinct Groups) all belong to Group V by the adrenalin test. 2 of these cases are now found to be schizophrenics—the other 4 are schizophreniform states.

We have not in our 2 series of examinations (schizophrenic patients and a mixed material of schizophrenias, schizophreniform states, and neurotics) found any typical response patterns for the various groups of diseases, and our experience hitherto is that the tests cannot give us any definite lines along which to proceed for the splitting up of the "clear-cut schizophrenics" and the "schizophreniform states". Neither can the method in our cases be said to be of any definite prognostic value.

SUMMARY

The experiments of *Funkenstein et al.* with epinephrine and mecholyl on mentally ill patients are mentioned. Also the work of *Alexander,* who has studied the pretreatment test results with the outcome of the therapy, is referred to.

The results arrived at are retested, especially as regards schizophrenia and schizophreniform states.

A material of 30 "clear-cut schizophrenics" are tested. Another material, also consisting of 30 patients, belonging to various illness groups, especially schizophreniform cases, has been examined.

We have not found any typical responce pattern for the various groups of illnesses. The test have not given us any definite lines along which to proceed for the splitting up of schizophrenia and the schizophreniform states, and can not be said to have had any definite prognostic value.

Different precautionary rules on carrying out the tests are stressed.

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